Short report

Action of cyproheptadine in spastic paraparetic patients

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SUMMARY The antiserotonergic agent cyproheptadine was evaluated in six patients as a medication for the management of spasticity due either to spinal cord trauma or to multiple sclerosis. Oral doses of cyproheptadine were progressively increased from 6 mg to 24 mg per day. Trial periods extended from 4 to 24 months and included a placebo substitution period. Cyproheptadine was found to decrease significantly the spontaneous and elicited ankle clonus in all six patients and spontaneous spasms in five patients. Cyproheptadine decreased the EMG activity and the dynamic strength produced by the knee extensor and flexor muscles during isokinetic movements in two of the four patients evaluated objectively. Subjectively, however, the patients did not report diminished strength.

An important role of 5-hydroxytryptamine (5-HT) in the modulation of spinal reflexes has been suggested from the results of biochemical, histochemical and physiological studies.¹⁻⁴ In a recent series of animal experiments we have demonstrated a progressive increase in sensitivity to exogenously administered 5-hydroxytryptophan (5-HTP), the precursor of 5-HT, after spinal cord transection. In these animals, cyproheptadine, a serotonergic antagonist, completely blocked the facilitatory effect of 5-HTP on spontaneous EMG activity.⁵⁻⁷ Since these results suggested a possible role of cyproheptadine in the control of spasticity in man, a pilot study was undertaken.

Patients and methods

The effect of cyproheptadine as an antispastic agent was evaluated with informed consent in six patients (five men and one woman). Patient characteristics are given in the table. The patients selected presented signs of spasticity due

to a traumatic lesion of the spinal cord or multiple sclerosis. In the latter cases, we could not rule out lesions elsewhere in the central nervous system, although lesions of the descending spinal pathways appeared to play a major role in the motor dysfunction. We were especially interested in patients who suffered from frequent spontaneous episodes of clonus or from massive spasms in the lower extremities.

Cyproheptadine was administered orally with an initial dosage of 12 mg/day and gradually increased to a maximum of 24 mg/day. The duration of the therapy varied from 4 to 24 months. In four of the patients, cyproheptadine was substituted by a placebo for a few days during the first month of therapy. One patient was kept on dantrolene sodium, 300 mg daily and another on baclofen 70 mg daily.

Muscle strength during maximal voluntary isokinetic knee movements was measured in four patients with the Cybex II dynamometer. The moment of the force (torque in Newton-meters) was measured as the knee moved from 90° of knee flexion to full extension for extension movements or vice versa for flexion movements at three different angular velocities. Measures of torque and angle were taken during three repeated maximal voluntary isokinetic movements at each of three velocities (30°/s, 90°/s and 180°/s) and the curve of the changes of torque with the angle of the movement was displayed on a Tektronix storage oscilloscope. Corrections were made for the gravitational torque due to the weight of the leg and apparatus.

The electromyographic (EMG) activity obtained with Beckman surface electrodes (16 mm) was recorded from five muscles; vastus medialis (VM), vastus lateralis (VL), medial hamstrings (MH), lateral gastrocnemius (LG) and tibialis anterior (TA) concomitantly with the strength and knee angle recordings during the maximal voluntary and

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Table Summary of results in individual patients

Patient, sex (age yr)	Aetiology (duration of disability in years)	Duration of treatment with cyproheptadine (months)	Effects of cyproheptadine		
			Ankle clonus	Spasms	Walking
M (23)	Cervical cord injury (2)	24	MR	MR	improved
M (24)	Cervical cord injury (10)	6	MR	—	improved
M (36)	Multiple sclerosis (8)	18	MR	MR	—
F (50)	Multiple sclerosis (5)	4	MR	MR	improved
M (48)	Multiple sclerosis (6)	6	SR	MR	improved
M (34)	Multiple sclerosis (10)	4	SR	MR	—

MR: Marked reduction or disappearance.

SR: Slight to moderate reduction.

passive movements. The myosignals were fed into a Grass model 7P3 pre-amplifier, amplified and recorded as unintegrated "raw" EMG or rectified and time averaged with a time constant of 0.2 s (IEMG).⁸ The level of co-activation in antagonistic muscles was determined by a co-activation index.⁹ The index was defined as the ratio of the peak amplitudes of the IEMG of the same muscle acting as agonist and as antagonist during maximal voluntary isokinetic movements at 30°/s.¹⁰

Each patient was requested to keep a daily log of the number of episodes of knee or ankle clonus and of the number of spontaneous spasms. Some aspects of autonomic function (for example frequency of micturition) were also noted.

Results

As illustrated in the table, cyproheptadine almost abolished ankle clonus in four patients and substantially reduced it in the other two. Spontaneous spasms of the lower extremities present in five patients almost disappeared. An example of the beneficial effect of cyproheptadine (Patient I) is given in fig 1. Administration of a placebo did not reproduce this effect. Figure 2 shows examples of the change in dynamic strength (moment, A, C) and electromyographic activity (IEMG, B, D) in the vastus lateralis muscle (VL) during maximal

Fig 1 Average number of beats of clonus elicited by two passive dorsiflexions of left ankle (above) and number of flexor spasms (below) recorded by patient (Case 1) during a 44 day period (x-axis). Arrows indicate from left to right: end of control period, intervals of cyproheptadine therapy at 12 mg/day, 16 mg/day, 24 mg/day, a substitution placebo period, and a return to cyproheptadine 24 mg/day.

Fig 2 Comparison of torque-angle and EMG activity patterns during maximal voluntary isokinetic knee extension movements at 30°/s in four spastic patients, three men and one woman with normal values before (A and B) and during (C and D) cyproheptadine therapy. Knee angle is given on the x-axis. In A and C, torque in Newton-meters is given on the y-axis. Mean torque-angle curves (solid lines) are derived from 19 healthy women, and mean peak torque is given in brackets on the y-axis. In B and D average EMG in percent of maximum is given on y-axis. Mean values (solid lines) are derived from 17 healthy women and the mean normal peak activity given in brackets on the y-axis for vastus lateralis (B) and (D). Vertical bars indicate ± 1 SD from the mean for torque in A and C and EMG activity in B and D.

voluntary isokinetic knee extension movements at 30°/s in four patients (the four curves in dotted lines). The curves were obtained before (A and B) and during (C and D) cyproheptadine therapy. In all cases they are compared to normal values: these are mean curves (solid line, ± 1 SD obtained in a group of healthy women).¹⁰ Before cyproheptadine (A), it can be seen that three patients produced less torque and EMG activity than normal women.

During cyproheptadine therapy (C), the peak torque values decreased in three of the four patients. The values at 45° knee angle, also decreased in the three patients by 33.3%, 48.4%, and 21.6% in cases 2, 1 and 4 respectively and was unchanged in one patient (case 3). It can also be observed that the shape of the torque-angle curves changed with therapy. For flexion movements at 30°/s, changes in the amplitude of the torque-angle curve with therapy were less

marked. One patient demonstrated a decrease of 33.3% in torque at 45° knee angle, while in the three other patients little change was seen. The reduction in torque was even more evident at 90° and 180°/s.

During cyproheptadine therapy (D), the peak EMG amplitude in the VL muscle decreased by more than 20% in two of the four patients and, in the other two it increased by more than 20%. The shape of the curve is, however, closer to normal. In the flexor (MH) muscle a decrease greater than 20% was seen in the peak of EMG activity in three of the four patients.

The co-activation index in the medial hamstrings muscle during maximal voluntary isokinetic knee extension movements at 30°/s varied from 26.7 to 45.8 before therapy. These values were higher than mean values reported in healthy women (7.5 ± 4.7 (SD), $N = 15$).⁸ In the vastus lateralis muscle during knee flexion movements the index varied from 16.7 to 74.2 in contrast to normal values of 11.4 ± 5.1 (SD), $N = 17$. During cyproheptadine therapy this index was unchanged ($\pm 20\%$) in three patients and increased in one patient in the VL. In the MH, the co-activation index was increased by more than 20% in two patients and unchanged in two.

Discussion

In the present study the oral administration of cyproheptadine substantially reduced the signs associated with spasticity in six patients. The antispastic action of cyproheptadine can be explained tentatively by its antiserotonergic activity as demonstrated in our animal experiment.⁵⁻⁷ Histological^{2 11 12} and electrophysiological¹³ evidence point to a direct effect of serotonin on motoneurons. One possible action of cyproheptadine is thus the blockade of the stimulating effect of 5-HT on motoneurons. It is probable in fact that in our six patients the descending 5-HT pathways were at least partly preserved since the spinal cord lesions were incomplete and a demyelinating process should not be expected to affect small and slow conducting fibres believed to constitute the 5-HT pathway. Interestingly, Davidson *et al*¹⁴ have reported a reduction in the 5HIAA levels in the lumbar CSF of spastic patients suffering from multiple sclerosis. This could be interpreted as an adaptive phenomenon to reduce stimulation of the disinhibited motoneurons. In this context cyproheptadine would further reduce this unnecessary stimulation. If 5-HT increases the excitability of the motoneurons directly, then cyproheptadine, by reducing this excitatory input, could increase the threshold of the motoneurons and consequently reduce the spatial and temporal recruitment necessary to produce movement. This mechanism could explain the reduction in dynamic

strength and EMG amplitude observed after cyproheptadine therapy. The reduced dynamic strength, however, was more than compensated by the reduction in spasms and clonus and the net functional result was an increased ability to walk in four patients.

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