Effect of baclofen upon monosynaptic and tonic vibration reflexes in patients with spasticity

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SUMMARY Measurements of monosynaptic reflex activity were made in 10 patients with spasticity before and during treatment with baclofen. There was evidence of both central sensory facilitation and increased fusimotor drive in untreated patients compared with controls. During treatment with baclofen, the central facilitation was reduced but there was no evidence of a reduction in fusimotor drive. The torque developed by vibration of the belly of the biceps and triceps muscles was not significantly different in 14 patients with spasticity compared with controls, and was not altered by treatment with baclofen despite clinical improvement in 12 of the patients. It is suggested that baclofen reduces the excitability of the monosynaptic reflex arc from dynamic spindles but does not affect the mechanisms responsible for the tonic vibration reflex.

Spasticity is characterized clinically by weakness of voluntary movement, increased muscle tone, and increased tendon reflexes. The increase in muscle tone during passive stretch is often 'clasp-knife' in character. Further disorders of reflex activity are manifested by the 'extensor' plantar response (dorsiflexion), which in severe cases may be part of a generalized flexion response in the lower limbs to stimulation of the skin of the foot or lower leg. Patients with severe spasticity frequently experience 'jumping' of the limbs or spontaneous clonus, and in addition may suffer painful reflex muscular contraction (cramps) in response to trivial sensory stimuli. These reflex disorders are difficult to quantify. One of the principal physiological abnormalities in spasticity is an increase in gamma motoneurone activity, lowering the threshold of the muscle spindles to stretching of the muscle. Phasic reflexes involving velocity-sensitive spindle organs and the monosynaptic reflex arc can be investigated clinically as indicated in the Figure. The amplitude of the compound muscle action potential associated with the ankle jerk (AJ) can be measured electromyographically and reflects both the mechanical sensitivity of the spindle organ—that is, gamma motoneurone drive—and the central excitability of the monosynaptic pathway. The H response, a muscle action potential indicating reflex muscular contraction obtained by electrical activation of incoming fibres from the spindle organs, is independent of gamma motoneurone drive. The action potential of the dromically evoked muscle twitch is the M response. In patients with spasticity the AJ is increased relative to the H response, confirming the presence of increased activity in gamma motor neurones (Angel and Hofmann, 1963). Although these measurements reflect the excitability of clinical tendon reflexes, they are a poor guide to the overall severity of spasticity in a given patient (Matthews, 1966). Muscle spindles (in particular those with Ia afferents) may also be activated tonically by vibration of the muscle reflexly initiating a contraction that builds up over the course of 20–30 seconds while vibration is continued. This response has been called the tonic vibration reflex (TVR) and in some ways resembles the phenomenon of post-tetanic potentiation (Eklund and Hagbarth, 1966). Although velocity-sensitive spindle organs are activated by both tendon tap and vibration, the strength of the TVR does not parallel the clinical activity of

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tendon reflexes (Hagbarth and Eklund, 1968) and it has been suggested that the TVR, like the tonic stretch reflex, could result at least partly from polysynaptic activation of alpha motoneurones (Matthews, 1972).

Gamma-aminobutyric acid (GABA) has been shown to produce an inhibitory effect upon spinal neurones, producing membrane hyperpolarization similar to the actions of naturally-occurring inhibitory transmitters (Curtis, Hosli, Johnston, and Johnston, 1968). Baclofen is a derivative of GABA and was given to patients with spasticity by Bergamini, Riccio, and Bergamasco (1966) in the hope that the spinal neurones involved in spastic reflexes would be suppressed and that this would help the patients. This hope proved to be justified and a number of confirmatory clinical reports have appeared (Pederson, Arlien-Søborg, Grynderup, and Henrikson, 1970; Jones, Burke, Marosszék, and Gillies, 1970; Hudson and Weightman, 1971). Electromyographic studies have shown that baclofen diminishes both the length-dependent stretch reflex and, to a lesser extent, the velocity-dependent stretch reflex in the spastic quadriceps muscle (Burke, Andrews, and Knowles, 1971). The latter authors reported that clinical evaluation after treatment showed no change in the tendon jerks of their 10 patients, despite a reduction in clonus, and suggested that the discrepancy between the effect of baclofen upon tonic and phasic stretch reflexes could be explained if baclofen depressed all spinal synapses, a larger number of synapses being involved in tonic than in phasic stretch reflexes.

The purpose of the present study was to ascertain more precisely the effect of baclofen upon reflexes known to be initiated by velocity-sensitive spindle organs (Figure)—that is, monosynaptic phasic reflexes and the TVR. The reduction in clonus that occurs during treatment suggests that monosynaptic activity has been reduced. Secondly, if it is true that the TVR is a polysynaptic phenomenon, diminution of the TVR should be more pronounced than diminution of the phasic reflexes. Thirdly, a study of the effect of baclofen upon the reflex system shown in the Figure might also provide evidence of the effects of baclofen, if any, upon dynamic fusimotor activity.

**METHODS**

**SUBJECTS STUDIED** Eight male and six female patients with spasticity were studied. Their mean
age, height, and weight are shown in Table 1. Patients were selected who could comfortably and willingly submit to testing, and who retained reasonable voluntary power despite a moderate to severe increase in muscle tone. Eight of the patients had multiple sclerosis, four had cervical spondylosis, and two had hereditary spastic paresis. All the patients had spasticity (increased tone with increased tendon reflexes and extensor plantar responses) in both legs. Some of the upper limbs studied were not spastic; of the patients' 28 arms, 21 had spasticity, five had an increase in tendon reflexes but no increase in tone, and two had no evidence of spasticity. Control values were obtained from two groups of normal subjects (Table 1) containing a similar proportion of males to females. The full control data have been presented in a previous report (McLellan, 1973).

**Clinical Examination** A full history was taken and the frequency and severity of muscle cramps, jerking of the limbs, and spontaneous clonus were noted. These patients were examined and the muscle tone in all four limbs was assessed clinically on a five-point scale, from 0 (normal tone) to 4 (very severe spasticity). The tendon reflexes also were evaluated on a five-point scale from 0 (absent) to 4 (clonus). Clinical and reflex assessments of the patients were made in the untreated state and during treatment with baclofen, which was administered orally in four divided doses totalling 20 to 100 mg daily. A second assessment was made at least 48 hours after the maximum dosage of baclofen had been reached. The TVR was examined in all 14 patients and phasic reflex activity was measured in 10 of them.

**Measurement of Phasic Reflex Activity** The methods used to activate and record the reflex activity have been described in detail in a previous report, and provide consistent and repeatable recordings from the same subject measured on different occasions (McLellan, 1973). The phasic responses were measured in the gastrocnemiussoleus muscle. The subject lay prone with the knee flexed at 30°, the lower leg resting on a padded ramp. The reflex contraction of the muscle was recorded with surface skin-clip electrodes 3 cm apart, connected to a Hewlett-Packard EMG amplifier system and storage oscilloscope (Electromyograph 1510A). The ankle jerk was obtained by striking the achilles tendon with a manually operated hammer, the head of which contained an electrical switch that triggered the oscilloscope when the tendon was struck. The force of the blow was chosen to obtain maximal AJ responses. H responses were obtained by stimulating the median popliteal nerve in the popliteal fossa with surface stimulating electrodes 3 cm apart, the cathode being proximal to the anode. A square wave electrical stimulus lasting 1 msec was used, the voltage being adjusted to obtain a maximal H response whether or not a small M response was also present. Both the AJ and the H responses were obtained 20 times at intervals of 20–30 seconds, alternate responses being reinforced by the Jendrassik manoeuvre. The peak-to-peak amplitudes of the mean AJ, reinforced AJ (AJR), H response (H), reinforced H response (HR), and maximal direct twitch response of the muscle (M) were recorded.

**Tonic Vibration Reflex** The method used to elicit the TVR has been described in detail in a previous report (McLellan, 1973). The patient was seated comfortably in a chair and the arm supported in an adjustable load-measuring splint, the elbow being flexed by 30°. The biceps and triceps muscles were vibrated in turn by a Pifco vibrator operating at maximum amplitude (approximately 2 mm) at 50 Hz, applied to the belly of the muscle. The torque developed by the muscle in response to vibration was detected by four metal foil strain-gauges in the rig and measured electronically, enabling readings to be made with an accuracy of ±0.05 lb f. ft. The mean of two or three measurements of each muscle was taken as the torque value. The results were analysed statistically using Student's t test to compare patients with controls and the paired t test to compare patients before and after treatment.

**Results**

**Clinical Effect of Baclofen** Clinical improvement was most pronounced in patients...
with multiple sclerosis and least in those with hereditary spastic paresis. Baclofen caused less sedation than would have been expected from comparable doses of diazepam but it did nevertheless have a tranquilizing effect; most patients commented that they slept better when on baclofen than when untreated and that this was due partly to a feeling of calmness as well as a reduction in the frequency of nocturnal cramps and jerking of the limbs. No patient reported improvement in the function of the upper limbs but 12 felt that their legs were less stiff, particularly in the mornings when spasticity tends to be most pronounced. On examination muscle tone was found to be diminished after baclofen by at least one clinical point in 10 of the patients and clonus was either reduced or abolished. Two patients had had frequent extensor spasms that were virtually abolished by treatment. The tendon reflexes were unchanged clinically in most patients, except for the reduction in clonus. All except two patients with disseminated sclerosis and one with cervical spondylosis have elected to continue with long-term baclofen treatment.

**PHASIC REFLEXES** The brisk tendon jerks in the patients with spasticity were reflected in the AJ/M ratio of 25.4% which was significantly greater than the control value of 14.3% (P < 0.05). The H/M ratio was also greater in the patients, indicating central facilitation of an incoming volley in Ia afferent nerve fibres. The mean AJ/H ratio (an index of gamma motoneurone drive) was increased, as expected, in patients with spasticity compared with controls (Table 2) but this difference was not statistically significant because of the considerable between-subject variation in the AJ/H ratio.

The effect of baclofen was to reduce the AJ/M and H/M ratios towards normal (P < 0.01, Table 2). This indicates a decrease in the motoneurone pool available for activation by an incoming Ia volley. There was an increase in the mean AJ/H ratio and in the effect of reinforcement by the Jendrassik manoeuvre but these changes were not statistically significant.

**TONIC VIBRATION REFLEX** The untreated patients developed a greater torque in response to vibration of the biceps and triceps muscles than the controls, but the difference was not statistically significant (Table 3). The position of the arm during vibration was such as to reduce the TVR of the triceps relative to the biceps, so that no valid comparison between the effects of vibration of flexor and extensor muscles can be made. No change was seen after treatment with baclofen. The TVR of the biceps was independent of muscle tone and of tendon reflex activity in the various arms studied; arms that showed clinical changes with baclofen showed no consistent change in their TVR.

**DISCUSSION**

The clinical effects of baclofen reported in this study are in accord with the previous reports mentioned above. Baclofen is of considerable value in the relief of spasticity, particularly when the patient is afflicted by painful cramps, spontaneous clonus and ‘jumping’ of the limbs. Its

| TABLE 2 |
|-----------------|------------------|------------------|
| **RATIOS (EXPRESSED AS PERCENTAGE) BETWEEN MEAN AMPLITUDES OF ANKLE JERK (AJ), REINFORCED ANKLE JERK (AJR), H RESPONSE (H), REINFORCED H RESPONSE (HR), AND M RESPONSE (M) IN CONTROL SUBJECTS AND IN PATIENTS WITH SPASTICITY BEFORE AND AFTER TREATMENT WITH BACLOFEN** |
| **Ratio %**     | **Controls**     | **Patients**     |
| ****            | **Untreated**    | **After baclofen** |
| AJR/AJ          | 157-3            | 127-7            |
| HR/H            | 122-5            | 112-4            |
| AJ/M            | 14.3             | 25.4             |
| H/M             | 22.4             | 30.2             |
| AJ/H            | 70-6             | 103-3            |

| TABLE 3 |
|-----------------|-----------------|-----------------|
| **TORQUES DEVELOPED AT WRIST DURING Vibration OF BICEPS AND TRICEPS MUSCLES** |
| **Muscle tested** | **Controls** | **Patients with spasticity** |
| ****               |              | **Untreated** | **After baclofen** |
| Torque developed in biceps muscle (lb ft fi) | 0.62 | 1.04 | 1.00 |
| Torque developed in triceps muscle (lb ft fi) | 0.35 | 0.48 | 0.40 |

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Sedative effect is relatively mild, the most troublesome side-effect being a tendency to increase weakness of the limbs if an excessive dose is used. Baclofen would be expected to increase the effectiveness of voluntary contraction only if reflex contraction of antagonistic muscles were impairing movement, which is not the case in all patients with spasticity. Nevertheless, the patients in this study who previously had tried diazepam for their spasticity expressed a marked preference for baclofen because of its greater effectiveness and the relative lack of sedation. The lack of a clinical change in tendon reflexes has been confirmed, but clinical grading is of course a crude method of assessing the extent to which tendon reflexes are increased and the lessening of clonus is in accord with the present electromyographic evidence that baclofen reduced the excitability of the motoneurone pool to an incoming volley along Ia afferent fibres.

The relationship between the strength of an incoming volley and the response of the motoneurone pool is unlikely to be linear. The size of the available motoneurone pool is limited so that a set amount of facilitation—as, for example, by the Jendrassik manoeuvre (Gassel and Diamantopolous, 1966)—would facilitate a small incoming volley proportionally more than a large one. The effect of reinforcement by Jendrassik’s manoeuvre (AJR/AJ and HR/H ratios, Table 2) was reduced in untreated patients compared with controls but it increased after the administration of baclofen. The reduced capacity for reinforcement of the H response in untreated spasticity is consistent with the view that the monosynaptic reflex loop is already in a facilitated state, permitting a proportionally smaller change in central facilitation by Jendrassik’s manoeuvre. The reduction of this facilitation by baclofen would therefore be expected proportionally to increase the effect of Jendrassik’s manoeuvre. The present observations also indicate that baclofen inhibited monosynaptic reflex activity more than it inhibited the pathways mediating Jendrassik’s manoeuvre. Baclofen did not appear to reduce the activity of gamma motoneurones.

Methodological factors affecting the TVR have been reviewed by Eklund and Hagbarth (1966). The physical characteristics of the patients’ limbs are also important in determining the torque developed during vibration: muscular arms, but more particularly arms with little subcutaneous fat, develop the greatest torques. The patients with spasticity were on average slightly smaller and lighter than the controls (Table 1) which could account for their slightly increased response to vibration compared with controls, the difference between the groups not being statistically significant.

The present study provides further information about the relationship between the stretch reflex, the tendon jerk, and the TVR in spasticity. Both the stretch reflexes and the tendon jerks are abnormal in spasticity, although the H/M ratio in itself is a poor guide to the severity of spasticity in a given patient (Matthews, 1966). The torque generated by the TVR does not parallel the activity of tendon reflexes or stretch reflexes in spasticity (Lance, de Gail, and Neilson, 1966; Hagbarth and Eklund, 1968). The TVR has been found to develop more rapidly than normal in patients with spasticity (Burke, Andrews, and Lance, 1972) which may reflect the increased excitability of the monosynaptic arc, but there is no evidence that the torque developed by the TVR is significantly increased in patients with spasticity. This is in contrast with the increased torques found in rigidity (McLellan, 1972, 1973). The inhibitory effect of baclofen upon the polysynaptic stretch reflex in spasticity is more pronounced than its effect upon the monosynaptic tendon reflexes (Burke et al., 1971). The present findings show that baclofen has no effect upon the strength of the TVR even in patients whose monosynaptic reflexes have been depressed.

In conclusion, the present observations indicate that baclofen reduces the amplitude of monosynaptic phasic reflexes by depressing the excitability of the reflex arc from velocity-sensitive spindle organs. The TVR was not increased in spastic limbs despite the increased tonic and phasic stretch reflexes—that is to say, monosynaptic reflex excitability does not determine the strength of the TVR. Moreover, the TVR was unaltered by baclofen despite a decrease in tonic and phasic stretch reflexes, indicating either that baclofen does not reduce the activity of all spinal cord synapses as suggested by Burke et al. (1971) or that the TVR is not a polysynaptic phenomenon.
I wish to thank the patients for their cooperation and Professor J. A. Simpson for his encouragement and advice. Baclofen was kindly supplied by Ciba-Geigy Laboratories, Horsham, Sussex.

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*J Neurol Neurosurg Psychiatry* 1973 36: 555-560
doi: 10.1136/jnnp.36.4.555

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