Modulation of the transmission in group II heteronymous pathways by tizanidine in spastic hemiplegic patients

E Maupas, P Marque, C F Roques, M Simonetta-Moreau

Objective: To investigate the effect of tizanidine (an α2 noradrenergic agonist) on transmission in the interneuronal pathway coactivated by group I and group II afferents in post-stroke patients with spastic hemiplegia.

Methods: Early and late facilitation of the quadriceps H reflex elicited in the common peroneal nerve—attributed to non-monosynaptic group I and group II excitation, respectively—was investigated in 14 spastic hemiplegic patients. All received a single dose of tizanidine (150 µg/kg) or placebo in randomised order at 10 day intervals. Repeated measurements were made at baseline (T0), 45–90 min, and 120 min after drug intake. Spasticity was assessed by modified Ashworth score in the quadriceps muscle and by a leg tone score calculated by the sum of the modified Ashworth score in five muscle groups.

Results: On the spastic side a decrease in late group II and, to a lesser extent, early group I common peroneal nerve induced quadriceps H reflex facilitation occurred with tizanidine (group II, mean (SEM) difference T0–T90: 34.3 (10.2)%, p<0.001; group I, T0–T120: 19.8 (9)%, p<0.05), but not with placebo (group II, difference T0–T90: 12.5 (8)%, NS; group I, T0–T120: 3.2 (7)%, NS). Tizanidine but not placebo decreased the quadriceps muscle and global lower limb Ashworth scores (2.9 (0.2) to 1.9 (0.3), p<0.001; and 12 (0.7) to 9.5 (0.8), p<0.0001, respectively).

Conclusions: Enhancement of group II–group I facilitation of the quadriceps motor neurones on the spastic side of hemiplegic patients is mediated by α2 noradrenergic agonists. This strengthens the view that late facilitation of quadriceps motor neurones is mediated by group II afferents and suggests that group II pathways may be involved in lower limb spasticity.

Facilitation of transmission in the lumbar interneuronal pathway coactivated by group II and group I afferents has recently been shown in a group of 20 patients with spastic hemiplegia.1 It has been suggested that a change in the descending control of the relevant premotor neurones might account for these results, and that the increased excitability of interneurones coactivated by group II and group I afferents could contribute to the pathophysiology of spasticity. Convincing evidence has been accumulated in the cat2–5 as well as in man6 for descending inhibitory monoaminergic control of this pre-motor neuronal system, which is specific to group II afferents. Noradrenaline, α2 agonists (tizanidine, clonidine), and their precursor L-dopa selectively depress the transmission of group II inputs in the pathways of lumbar premotor neurones.2–5

Our aim in this study was to investigate the effect of oral administration of an α2 noradrenergic agonist (tizanidine) or placebo on common peroneal nerve induced early group I and late group II quadriceps H reflex facilitation in patients with spastic hemiplegia. Modulation of the hyperexcitability of the group II–group I premotor neuronal lumbar pathway by tizanidine would provide further evidence that this system plays a role in the pathophysiology of spasticity.

METHODS

Subjects

The experiments were carried out on 14 post-stroke patients with hemiplegia (eight men and six women, eight right and six left hemiplegias, mean age 53.7 years (range 21 to 70)). The subjects gave their informed consent to the experimental protocol, which was approved by the local ethics committees.

The patients were selected on the basis of the following criteria: first, that they had a first right sided or left sided motor deficit of abrupt onset affecting the leg and caused by a single vascular lesion (ischaemia (11) or haematoma (3)) in the territory of the middle cerebral artery; and second, that they had spasticity of the quadriceps muscle assessed by the modified Ashworth scale and present for less than one year (between 2 and 12 months in all the patients studied). We excluded patients with defective oral comprehension, hepatic insufficiency, renal insufficiency, recent myocardial infarction, hypotension, or receiving antispastic treatment at the screening visit. Only one patient had been treated with an antispastic drug around the time of the study, but it was stopped several weeks before the study began.

The motor deficit was assessed at a screening visit using three validated indices: the trunk control test, the motricity index, and the modified Ashworth scale.7 Leg tone was assessed by the sum of the Ashworth scores of five groups of muscles: hip adductors, knee flexors (hamstrings) and extensors (quadriceps), ankle flexors, and ankle extensors.

The clinical features and assessment of the leg spasticity of the 14 hemiplegic patients are summarised in table 1. The mean (SEM) dose of tizanidine given was 9.85 (1.66) mg (range 7 to 13).

Experimental procedure

General experimental arrangement

The subjects were comfortably seated in an armchair with the hip semi-flexed (60°), the knee slightly flexed (10–20°), and the ankle in 20° plantar flexion.
Electromyography (EMG) involved the use of surface electrodes 2 cm apart secured to the skin over the muscle belly of the vastocrureus (15–20 cm above the patella on the anterior aspect of the thigh) and the tibialis anterior (the medial part of the anterior aspect of the leg).

Quadriceps H reflex
The quadriceps H reflex was evoked by stimulating the femoral nerve percutaneously with rectangular shocks of 1 ms duration (0.33 Hz). The active cathode (a half ball 2 cm diameter) was placed in the femoral triangle and the reference electrode under the buttock. The intensity of the test stimulus was first progressively increased to obtain a stable maximum H reflex on the oscilloscope screen. The size of the test H reflex was adjusted at about 20% of its maximum amplitude during all the experiments. For each patient, seven intervals (interstimulus interval (ISI)) between the conditioning common peroneal nerve and the femoral nerve test were randomly alternated (8, 10, 12, 14, 16, 18, and 20 ms). For each delay studied, 20 unconditioned (control) and 20 conditioned reflexes were randomly alternated. The amplitudes of the reflex responses were measured peak to peak and analysed by computer on-line, the result being stored on disk for further analysis. Conditioned reflexes were expressed as a percentage of control reflexes.

Conditioning stimulus
Electrical pulses of 1 ms duration were delivered to the common peroneal nerve through bipolar surface electrodes (1 cm diameter silver plate electrodes 2 cm apart). The common peroneal nerve was stimulated at the level of the caput fibulae at a site where the threshold for the M response was lower for the tibialis anterior than for the peroneal muscles; there was, however, a response in the latter when the stimulation was increased to twice the motor threshold. The current was measured by a current probe (Textronic 602) and expressed in multiples of the intensity for the motor threshold (MT). We verified by tendon palpation that stimulation of the common peroneal nerve at twice motor threshold did not produce any contraction of muscles other than those innervated by that nerve—that is, it did not encroach upon another nerve.

Cutaneous stimuli
The cutaneous sensation (weak local or radiating paraesthesiae) evoked by common peroneal nerve stimulation was mimicked by pure cutaneous stimuli to estimate the contribution of the cutaneous afferents. The local sensation was reproduced by plate electrodes placed 3 cm more laterally than the nerve trajectory, or on the dorsal aspect of the foot over the nerve projection area (allowance was made for the extra peripheral conduction time). The stimulus intensity was adjusted to imitate the strong but not painful sensation evoked by common peroneal nerve stimulation at twice motor threshold.

Clinical evaluation
The modified Ashworth score of hip adductors and knee and ankle flexors and extensors was measured at the beginning and end of each experiment.

Experimental course
The electrophysiological tests were undertaken before and at 45, 90, and 120 minutes (T0, T45, T90, T120) after oral

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**Table 1** Clinical features of the 14 patients and doses of tizanidine given

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Duration (months)</th>
<th>Side of hemiplegia</th>
<th>Motricity index (/200)</th>
<th>Trunk cont test (/100)</th>
<th>Q tonus (/3)</th>
<th>Leg tonus (/25)</th>
<th>Tizanidine dose (mg)</th>
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<td>41</td>
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Cont, control; F, female; M, male; Q, quadriceps.

**Table 2** Comparison of the mean H max/M max ratio and the mean H/M intensity ratio thresholds before and after tizanidine or placebo on the spastic and non-spastic sides

<table>
<thead>
<tr>
<th></th>
<th>Before tizanidine</th>
<th>After tizanidine</th>
<th>Before placebo</th>
<th>After placebo</th>
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<td>Spastic side</td>
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<tr>
<td>H max/M max ratio</td>
<td>0.68 (0.1)</td>
<td>0.67 (0.16)</td>
<td>NS</td>
<td>0.7 (0.13)</td>
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<td>H/M intensity</td>
<td>0.92 (0.06)</td>
<td>1.05 (0.06)</td>
<td>1.04 (0.09)</td>
<td>1.01 (0.09)</td>
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<tr>
<td>Non-spastic side</td>
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<td></td>
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<tr>
<td>H max/M max ratio</td>
<td>0.56 (0.13)</td>
<td>0.48 (0.14)</td>
<td>0.54 (0.09)</td>
<td>0.47 (0.07)</td>
</tr>
<tr>
<td>H/M intensity</td>
<td>1.08 (0.06)</td>
<td>1.17 (0.08)</td>
<td>1.11 (0.1)</td>
<td>1.1 (0.1)</td>
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</tbody>
</table>

Values are mean (SEM).
administration of 150 μg/kg of tizanidine, or placebo, successively in a single blind design. The order of administration of tizanidine or placebo was randomly determined for each patient. The interval between the first and second test was 8 to 10 days. Both the spastic and the non-spastic side were assessed in the same session at each measurement time.

Statistics
The dependent variable was the size of the conditioned quadriceps H reflex expressed as a percentage of control H reflex. Results are presented as mean (SEM). The Wilcoxon rank test was used for comparisons between the spastic and non-spastic sides. The non-parametric Friedman test was used to compare successive measurements at the different periods of the experiment. A comparison at baseline of the spastic and non-spastic sides, respectively, in the 14 patients from this study with the responses of a control group of 20 subjects from a previous study1 was also done (using a Mann–Whitney test), as we used the same electrode location, the same conditioning stimulus, and a similar size of unconditioned H reflexes in both studies. A probability (p) value of <0.05 was considered as significant. The correlation between the ranking on the Ashworth scale or on the quadriceps Ashworth score and the leg tone score in this patient decreased from 3 to 2 and from 13 to 11, respectively, after tizanidine but was not affected by placebo.

RESULTS
The comparison of the value of the mean H_{max}/M_{max} amplitude ratio and the mean H/M intensity threshold ratio before and after tizanidine or placebo showed no significant difference on either the spastic or the non-spastic side (table 2).

The variations in amplitude of the quadriceps H reflex after stimulation of the common peroneal nerve were assessed at different ISIs (8, 10, 12, 16, 18, and 20 ms, and sometimes 6 ms) on both sides in the 14 patients. Figure 1 shows the time course of facilitation of the quadriceps H reflex conditioned by common peroneal nerve stimulation at twice the motor threshold (expressed in a percentage of the control H reflex) in one hemiplegic patient on the non-spastic and spastic sides before (T0) and 90 minutes after (T90) administration of tizanidine or placebo. On the non-spastic side at baseline (T0) (dashed lines, filled triangles), common peroneal nerve stimulation evoked a biphasic facilitation of the quadriceps H reflex, as described in normal subjects.10 The early facilitation (ISI, 8–12 ms) peaking at 10 ms (167 (11)% of the control H reflex value) is attributed to the non-monosynaptic excitation of group I afferents.11 The late facilitation, peaking at 14 ms (163 (7)% of the control value) and decreasing progressively after 16 ms is attributed to excitation of group II afferents.10 On the spastic side at T0 (thick uninterrupted line, filled circles), a significant increase in the amount of both late group II and early group I facilitation was observed in comparison with the non-spastic side, as previously described in patients with spastic hemiplegia1 (ISI 14 ms: 254 (8)%; ISI 10 ms: 216 (15)% of the control value, respectively). Administration of 8 mg of tizanidine orally caused a substantial decrease in both group I and group II facilitation on the spastic side in this patient at T90 (fig 1, thin uninterrupted line, empty triangles) did not elicit any significant changes in either group I facilitation (ISI 10 ms: 206 (11)% of control value) or group II facilitation (ISI 14 ms: 281 (14)% of control value) in comparison with baseline (T0, spastic side) results. The quadriceps Ashworth score and the leg tone score in this patient decreased from 3 to 2 and from 13 to 11, respectively, after tizanidine but was not affected by placebo.

Similar significant tizanidine induced changes of group II facilitation were observed in all the 14 patients on the spastic side (at least for one interval of the late excitation). A smaller decrease in group I facilitation was observed in 11 of the 14 spastic patients.

As the time course of changes in quadriceps H reflex elicited by common peroneal nerve stimulation at 2×MT can be divided into early group I facilitation (ISI of 8, 10, and 12 ms) and later group II facilitation (ISI of 14, 16, 18, and 20 ms), statistical analysis was done by averaging the data across ISIs of 8 to 12 ms (group I facilitation) and 14 to 20 ms (group II facilitation).

The mean (SEM) values for group I (8–12 ms) and group II (14–20 ms) quadriceps H reflex common peroneal nerve induced facilitation in the spastic and non-spastic side of the 14 hemiplegic patients before and after placebo or tizanidine are given in fig 2. At baseline (T0), mean group I and group II facilitation was significantly increased on the spastic side, at 139.5 (9.7)% and 147.1 (10.2)%, respectively (fig 2A; Wilcoxon test, p<0.001) compared with the non-spastic side (120 (5.0)% and 117 (4.2)%, respectively (fig 2B)) or with the control group in our previous study1 (group I, 118.5 (3.6)%; group II, 118.4 (3.6)%; Mann–Whitney test; p<0.05 and p<0.0001, respectively). No statistical differences were observed between the non-spastic side and the control group.

After tizanidine there was a substantial decrease in late group II facilitation and to a lesser extent in early group I facilitation on the spastic side. The largest difference in mean group II facilitation was observed 90 minutes after administration of tizanidine (34.4 (10.2)% v baseline (p<0.001) for ISI of 14–20 ms) and 120 minutes after tizanidine for the early group I facilitation (19.8 (9.0)% v baseline (p<0.05) for ISI of 8–12 ms (fig 2A). On the non-spastic side (fig 2B), tizanidine induced a smaller decrease in group II and group I facilitation compared with the spastic side, and the difference...
from baseline amplitudes was not significant. Administration of placebo did not produce any change in early group I or late group II facilitation on either the spastic or the non-spastic side, whatever the delay between conditioned common peroneal and test femoral nerves studied, and whatever the period (T0, T45, T90, or T120) of the experiment (fig 2, C and D) (group II, difference T0–T90: 12.5 (8.0); group I, T0–T120: 3.2 (7.0); both NS).

The Ashworth score of the quadriceps muscle decreased from 2.9 (0.2) to 1.9 (0.3) (p < 0.001) after administration of tizanidine and did not change after placebo (from 2.8 (0.3) at baseline to 2.6 (0.3) post-placebo). A similar significant decrease in the global lower limb Ashworth score was also observed after tizanidine (from 12.1 (0.8) at baseline to 9.6 (0.9) post-tizanidine (p < 0.0001)) and was not observed after placebo (from 12.1 (0.8) at baseline to 12 (0.9) post-placebo).

A trend to a significant correlation (Spearman’s rank test) between the tizanidine induced changes in the conditioned quadriceps H reflex amplitude and lower limb spasticity was found: decrease in late group II facilitation at 14 ms interval v decrease in the global leg tone score, r = 0.52 (p = 0.053). There was no correlation between conditioned quadriceps H reflex amplitude and the motor impairment score (trunk control test and motricity index).

The effect of pure cutaneous stimulation of the skin above the caput fibulae or on the dorsal aspect of the foot mimicking the sensation elicited by common peroneal nerve stimulation at 2 × MT was tested in three patients. Cutaneous stimulation did not evoke any significant quadriceps H reflex changes on the spastic side at baseline or after tizanidine or placebo, whatever the period of the measurement.

Drug induced side effects
After oral administration of tizanidine, sleepiness occurred in all the 14 patients 45 minutes or later after the dose was given, leading to sleep of variable duration (range 30 to 105 minutes). All the patients had periods of wakefulness during their sleep. Four patients complained of dry mouth with tizanidine. No other adverse effects were observed. Sleepiness was observed with placebo in five patients.

DISCUSSION
Group II–group I facilitation at baseline
In normal subjects, stimulation of the common peroneal nerve evokes two peaks of facilitation in the quadriceps H reflex. The early low threshold peak is attributed to non-monosynaptic group I excitation. The characteristics of the second peak (higher threshold, late latency increasing more than that of the early peak when the common peroneal nerve is cooled) are consistent with a group II effect. Indirect arguments suggest that group I and group II excitations might be mediated through common interneurones in humans, as has been described in the cat. Recent human data have also suggested that these group II “premotor neurones” might be implicated in the control of locomotion.

In a previous group of 20 spastic hemiplegic patients, a significant increase in both group II and group I common peroneal nerve induced facilitation of the quadriceps H reflex was described on the spastic side compared with the unaffected side, or with either the right or the left side in 20 controls. This has been attributed mainly to facilitation of transmission in the group II–group I pathways. Similar results were obtained at baseline in the present group of 14
spastic hemiplegic patients. Moreover, using the same experimental paradigm, Rémy-Neris et al have also recently observed a greater heteronymous group II–group I facilitation in quadriceps motor neurones after stimulation of the common peroneal nerve in patients with spastic paraplegia compared with those reported in normal subjects. 1, 10

Tizanidine v placebo effect
In our study, tizanidine induced a marked decrease in late quadriceps H reflex facilitation evoked by stimulation of common peroneal nerve group II afferents, and a less pronounced decrease in early group I facilitation on the spastic side in our hemiplegic patients. A similar but smaller and non-significant modulation of early and late facilitation was observed on the non-spastic side after tizanidine. Although it has been suggested that part of the antispastic action of tizanidine may be supraspinal in origin, 16 its depressive action at spinal cord level on polysynaptic reflexes has been well documented in the spinal cat 19, 20 and more recently in patients with spastic paraplegia. 17 At spinal level, the decrease in heteronymous common peroneal facilitation of quadriceps motor neurones observed after tizanidine might reflect an alteration of the excitability of the monosynaptic reflex arc. The absence of any significant difference in the value of the mean \( H_{max}/M_{max} \) amplitudes and H/M intensity thresholds (assessing the response of quadriceps motor neurones to a input) before and after tizanidine suggests that the decrease observed after the drug was not caused by excitability changes in quadriceps motor neurones and could rather have taken place at an interneuronal level. Moreover, intravenous injection of clonidine — another \( \alpha_2 \) noradrenergic agonist —in the spinal cat enhances rather than weakens the excitability of \( \alpha \) motor neurones. 21

The results observed after tizanidine cannot be explained by modulation of the cutaneous afferent discharges because there was no significant contribution from cutaneous afferents to the bispastic common peroneal nerve induced quadriceps H reflex facilitation, either in healthy individuals or in hemiplegic patients. 4, 10 Control experiments done in this study confirmed that tizanidine had no effect on responses elicited by pure cutaneous stimuli mimicking mixed common peroneal nerve stimulation.

Because all 14 patients included in our study fell asleep after tizanidine, we need to consider the possible contribution of changes in vigilance to the modulation of common peroneal nerve induced quadriceps H reflex facilitation. The sedative effects of tizanidine are well known in normal subjects 22 and in patients with cerebral or spinal disorders. 23 In animal studies, both monosynaptic and polysynaptic spinal reflexes are depressed during desynchronised sleep. 24 In humans, the H reflex decreases during the early stages of sleep, is abolished during REM sleep, and briefly increases during wakefulness. 25, 26 In our study the duration of the period of sleepiness varied from patient to patient and occurred during the assessment of the spastic side as well as of the non-spastic side. Even if sleepiness contributed to the decrease in group II–group I facilitation observed after tizanidine, the differences between the spastic and non-spastic sides suggest that the drug has pharmacological effects on the spastic side that are not related to this side effect.

Tizanidine given by intravenous injection at doses of 150 \( \mu \)g/kg in anaesthetised cats strongly depresses group II but not group I postsynaptic potentials. 3 Similar results have been obtained with the application of noradrenaline or tizanidine by spinal iontophoresis. 8, 27 In humans the antispastic effects of tizanidine are unlikely to be associated with enhancement of excitability of spinal inhibitory interneurones receiving group I afferent projections. 27 In normal subjects, the spinal segmental reflex (medium latency response) mediated by group II muscle afferents evoked by stretch in ankle and foot muscles is selectively depressed by tizanidine, while the short latency response is unaffected. 24, 29 In this study, tizanidine induced a strong depression of group II facilitation on the spastic side of all hemiplegic patients, confirming the previous results obtained in animals and normal human subjects. Thus enhancement of group II facilitation observed on the spastic side in hemiplegic patients can be significantly modulated by an \( \alpha_2 \) noradrenergic agonist such as tizanidine. This strengthens the view that common peroneal nerve induced late facilitation of quadriceps motor neurones is mediated by group II afferents.

The simultaneous decrease in early group I facilitation observed in 11 of the 14 patients after drug intake, although less pronounced than group II tizanidine induced depression, is puzzling in view of the selectivity of monoaminergic descending inhibitory control on group II pathways in the cat. 7, 8, 13, 27 However, using the same common peroneal nerve stimulation—quadriceps H reflex facilitation in spastic paraplegic patients, Rémy-Neris et al have similarly observed a decrease in both oligosynaptic group II and group I facilitation after intrathecal administration of 60 \( \mu \)g of clonidine. 21 The finding that tizanidine also causes depression of early non-monosynaptic group I facilitation suggests that the tonic increase in excitability of the common group II→group I interneurones might in part reflect an increased efficiency of the group II background discharge. This greater tonic group II discharge from pretibial flexors (statically stretched because of the 20° plantar flexion) could be caused by hyperexcitability of static \( \alpha \) motor neurones. However, there is no evidence for a change in the activity of static \( \alpha \) motor neurones in spastic patients. 20, 21 Group II tonic discharge might be more efficient in such patients because it would not be gated by monoaminergic descending pathways that are disrupted by the central lesion.

Correlation with spasticity
Tizanidine caused a consistent decrease in lower limb spasticity as assessed by the Ashworth scale in all our patients. This confirms the antispastic effect of the drug, which has previously been shown in animal studies and in spastic patients. 20, 21, 30 Despite the fact that electrophysiological investigation on heteronymous group II projections from tibialis anterior onto quadriceps motor neurones, whereas spasticity was assessed clinically in homonymous pathways, we found a trend to a significant correlation between the decrease in the late group II facilitation at the 14 ms interval and the decrease in global leg tone. These results provide further evidence of a possible contribution of hyperexcitability of group II pathways in spasticity. However, it must be pointed out that in the patient illustrated in fig 1 tizanidine decreased group II→group I facilitation towards the level observed at baseline on the non-spastic side, and at the same time decreased but did not suppress lower limb spasticity as assessed by the Ashworth scale. This suggests that other mechanisms are involved in the production of spasticity, such as peripheral changes in the mechanical properties of the muscle. 34

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REFERENCES


