

Pharmacodynamics and pharmacokinetics of the oral antispastic agent tizanidine in patients with spinal cord injury

Christopher J. Mathias, MBBS, DPhil, FRCP; John Luckitt, MBBS; Pankaj Desai, MBBS; Harry Baker, MBBS, FRCS; Wagih El Masri, MBBS, FRCS; Hans L. Frankel, MBBS, FRCP

Department of Medicine, St. Mary's Hospital and Medical School, Praed Street, London W2 1NY, UK; University Department of Clinical Neurology, Institute of Neurology and National Hospital for Nervous Diseases, Queen Square, London, UK; National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks, UK

Abstract—The efficiency and duration of action of a single oral dose (8 mg) of tizanidine in patients with spinal cord injuries were determined by studying its antispastic, cardiovascular and sedative effects along with its pharmacokinetic profile in five tetraplegic and five paraplegic patients. After the administration of tizanidine, there was a reduction in spasticity in both groups within half an hour, with the effects lasting for 3 to 4 hours. There was no rebound increase in blood pressure. There was a greater increase in sedation in the tetraplegics than in the paraplegics. Plasma tizanidine levels rose within half an hour after dosing and peaked at one hour. The levels had fallen to 15 percent by 6 hours. The plasma half-life was 2.7 ± 0.06 hours. We conclude that oral tizanidine has antispastic effects in patients with spinal cord injuries without affecting the power of non-involved muscle groups. It has minimal effects on blood pressure and it lowers heart rate. Side effects include sedation and dryness of mouth.

Key words: *paraplegic, sedative, spasticity, spinal cord injury, tetraplegic, tizanidine.*

INTRODUCTION

Tizanidine (DS103-282) is an imidazole derivative which, on the basis of animal studies, diminishes spasticity by depressing polysynaptic reflexes, probably by antagonizing the excitatory actions of spinal interneurons (1,9). It is effective in reducing muscle tone in spastic patients (3,4). We investigated the pharmacodynamics and pharmacokinetics of tizanidine in patients with spinal cord injuries who had moderate-to-severe degrees of spasticity. Five tetraplegic patients (with spastic upper and lower limbs) and five paraplegic patients (with spastic lower limbs only) were studied. Assessments of muscle power were made in the intact limbs of paraplegics to determine if the drug was suppressing activity in unaffected limbs. Blood pressure, heart rate, and sedation were also measured, together with plasma levels of tizanidine.

PATIENTS AND METHODS

Five tetraplegics (four male, between 20 and 45 years) and five paraplegics (all male, between 18 and

Address all correspondence and requests for reprints to: Dr. C.J. Mathias, Pickering Unit, Department of Medicine, St. Mary's Hospital, Praed Street, London W2 1NY, UK.

Dr. Mathias is with the Dept. of Medicine, St. Mary's Hospital and Medical School, London; University Dept. of Clinical Neurology, Institute of Neurology and National Hospital for Nervous Diseases, London, and the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks.

J. Luckitt and P. Desai are with the Dept. of Medicine, St. Mary's Hospital and Medical School, London.

H. Baker, W. El Masri and H.L. Frankel are with the National Spinal Injuries Centre, Stoke Mandeville Hospital, Aylesbury, Bucks.

44 years) with closed chronic (over 12 months) traumatic spinal cord transection were studied. All had previously been treated for spasticity. In the majority, the drugs (diazepam and/or baclofen) had caused side effects or had been ineffective in reducing spasticity in doses devoid of side effects. All medication was withdrawn two weeks prior to the study. None of the patients had any other complications.

Studies were performed in a warm, well-lit clinical laboratory. All patients had a light breakfast without beverages.

Patients were studied while supine and horizontal on a comfortable bed. Spasticity was measured using the Ashworth Scale (**Table 1**). Muscle power was assessed using the Medical Research Council Scale (**Table 2**). Neurological assessment was performed throughout the study. Blood pressure was measured by an automated sphygmomanometer which provided a print-out of systolic and diastolic blood pressure and heart rate. This was compared, before each study, with a standard sphygmomanometer to ensure accuracy. Sedation was measured on a 100 mm bipolar analogue scale with "asleep" at one end, and "wide-awake" at the other end. Scoring was done by the patients. Patients volunteered side effects at intervals during the study. Blood for measurement of plasma tizanidine levels was taken from an intravenous indwelling cannula. For the later samples (1200 and 2400 hrs) venipuncture was used. Tizanidine was measured by radioimmunoassay using antibody raised in sheep. The inter-assay and intra-assay coefficient of variation was 5.8 percent and 4.4 percent respectively, for duplicate samples. There was no cross-reaction of main metabolites with antiserum, and the radioimmuno-

Table 1.

Clinical assessment of the degree of spasticity, using a modified Ashworth's Scale.

0	= Muscle tone normal.
1	= Slight increase in tone giving a "catch" when a limb moved in flexion or extension.
2	= More marked increase in tone, but limb easily flexed.
3	= Considerable increase in tone, passive movement difficult.
4	= Limb in flexion or extension.

Table 2.

Assessment of muscle power using the Medical Research Council Scale.

0	= No active contraction.
1	= Visible palpable contraction without active movement.
2	= Movement which is possible with gravity eliminated.
3	= Movement which is possible against gravity.
4	= Movement which is possible against gravity plus resistance but which is weaker than normal.
5	= Normal power.

assay was specific to unchanged compound in human plasma.

The protocol consisted of the patients coming up to the laboratory after breakfast. They were placed comfortably in a bed, and after a half-hour equilibration period, baseline measurements were begun. Three sets of pre-drug measurements were made at 15-minute intervals. Tizanidine 8 mg was then administered with 250 ml of water. Observations were continued at half-hour intervals for two hours, and then at hourly intervals for a further four hours. Repeat measurements were made 12 and 24 hours later when the patients were in the ward.

Measurements were repeated on a separate occasion in a similar manner, except that no drug was administered. In these studies, measurements of sedation and collection of blood were not included.

The protocol was approved by the Ethics of Research Committee of Stoke Mandeville Hospital. Paired and unpaired Student's *t*-tests and analysis of variance were used for statistical analysis. The results expressed are means \pm standard errors of the mean.

RESULTS

Antispastic effects

All had moderate-to-severe degrees of spasticity affecting the lower limbs. The tetraplegics also had spastic upper limbs. After tizanidine, there was a rapid and substantial reduction in spasticity (**Figures 1 and 2**): the peak reduction occurred between one and one-and-a-half hours in each group ($p < 0.05$ for

each). There was a greater reduction in spasticity in the upper limbs of the tetraplegics as compared to their lower limbs. By the fourth hour, lower-limb spasticity had returned to pre-drug levels. There was no rebound spasticity when measurements were made 12 and 24 hours after drug administration.

Muscle power

Tizanidine had no effects on muscle power in either group at any stage of the study. There was no impairment of muscle power in the intact upper limbs of the paraplegics.

Blood pressure

Systolic and diastolic blood pressure levels were similar in the tetraplegic and paraplegic patients (see **Figure 3**). After tizanidine, there was a statistically non-significant reduction of systolic blood pressure in both groups, with no change in diastolic blood pressure. There was no rebound increase in blood pressure during the period of observation. There was no significant change in systolic or diastolic blood pressure when no drug was administered.

Heart rate

The basal heart rate was higher in the paraplegics (see **Figure 4**). After tizanidine, there was a fall in heart rate in both groups ($p < 0.05$ after 1.5 hours). The lowest level in the tetraplegics was 58 ± 6 beats/min and in the paraplegics 70 ± 8 beats/min.

Sedation

There was an increase in sedation after tizanidine in both tetraplegics and paraplegics (see **Figure 5**). Sedation appeared greater in the tetraplegics, but there was considerable variability in readings. The peak levels of sedation were within the first hour with gradual waning, so that by the third hour most patients were fully awake.

Pharmacokinetics

Plasma levels of tizanidine rose within 30 minutes of drug administration and peaked after one hour. There was then a gradual mono-exponential decline. Levels were below 15 percent of the peak levels when measured six hours after drug administration. There were small but detectable

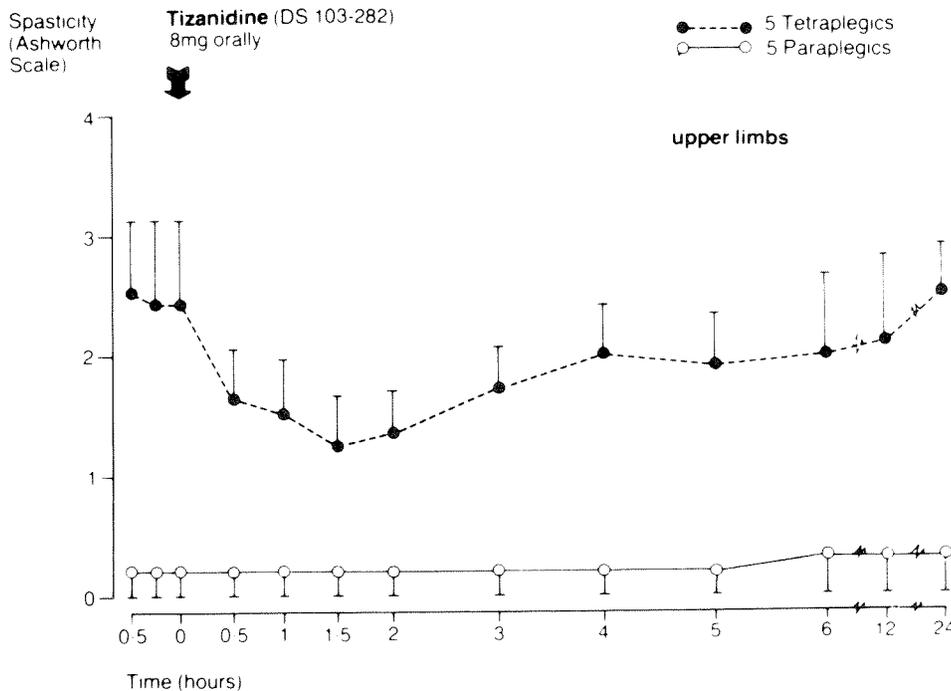


Figure 1.

Spasticity measured by modified Ashworth Scale (0—normal, 4—maximum spasticity) in the upper limbs of tetraplegic and paraplegic patients before and after tizanidine given at time 0. Bars indicate means + SEM.

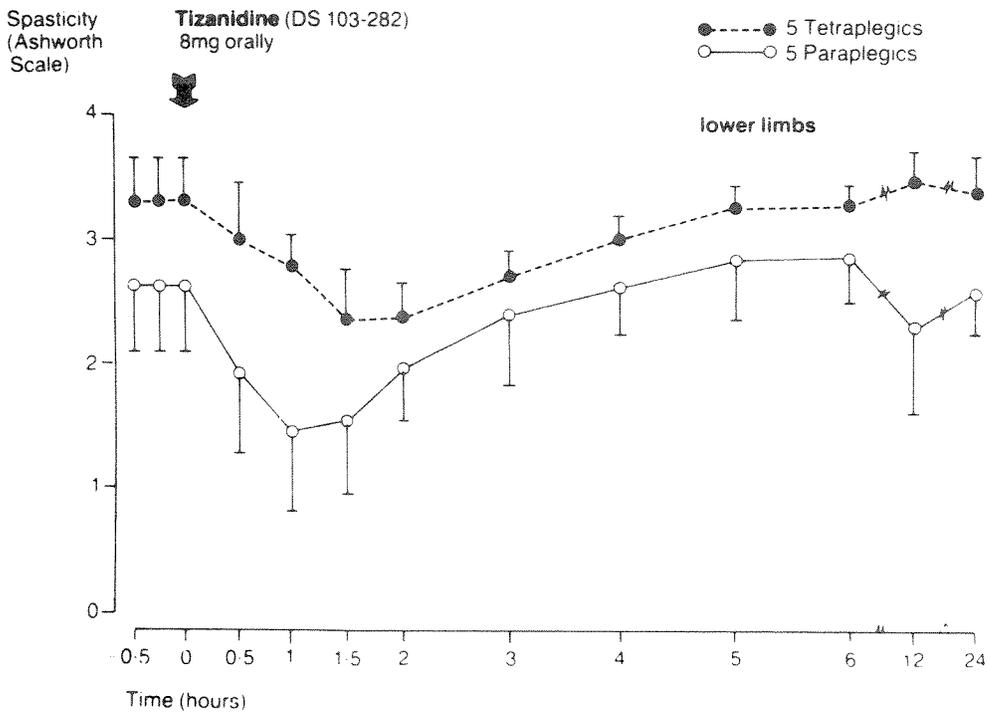


Figure 2. Spasticity measured by modified Ashworth Scale (0—normal, 4—maximum spasticity) in the lower limbs of tetraplegic and paraplegic patients before and after tizanidine given at time 0. Bars indicate means + SEM.

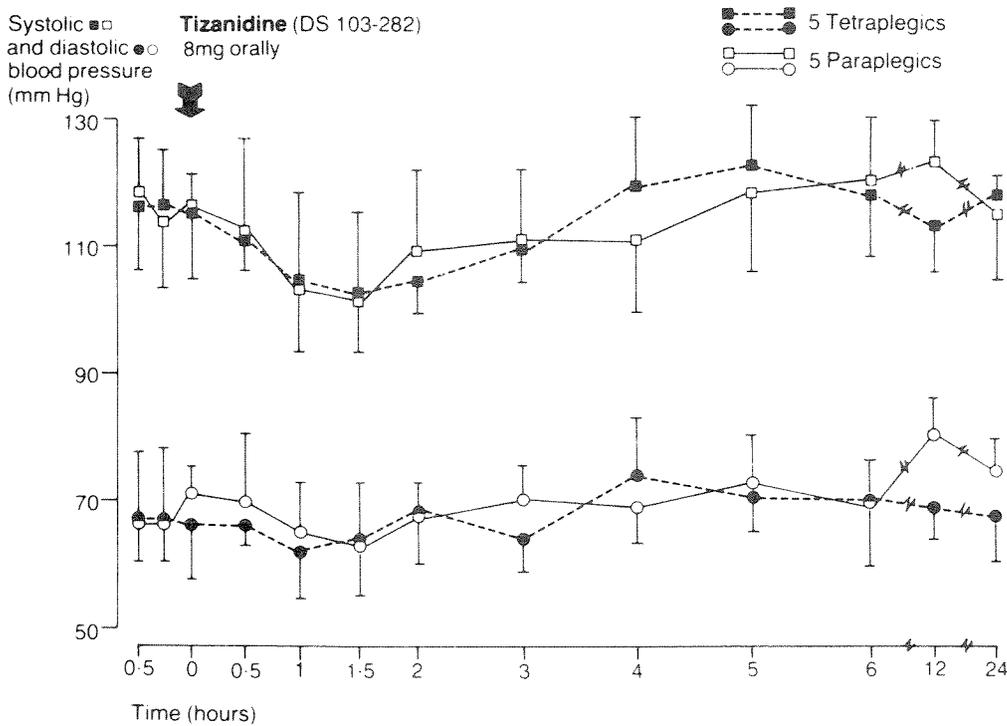


Figure 3. Systolic and diastolic blood pressure in tetraplegic and paraplegic patients before and after tizanidine given at time 0. Bars indicate means + SEM.

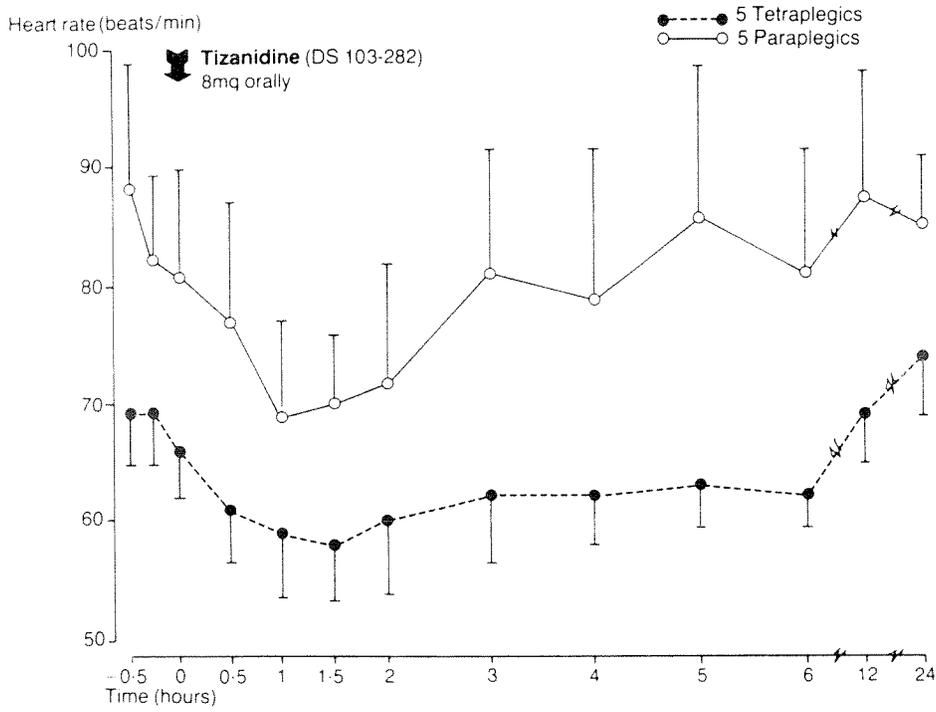


Figure 4. Heart rate in tetraplegic and paraplegic patients before and after tizanidine given at time 0. Bars indicate means + SEM.

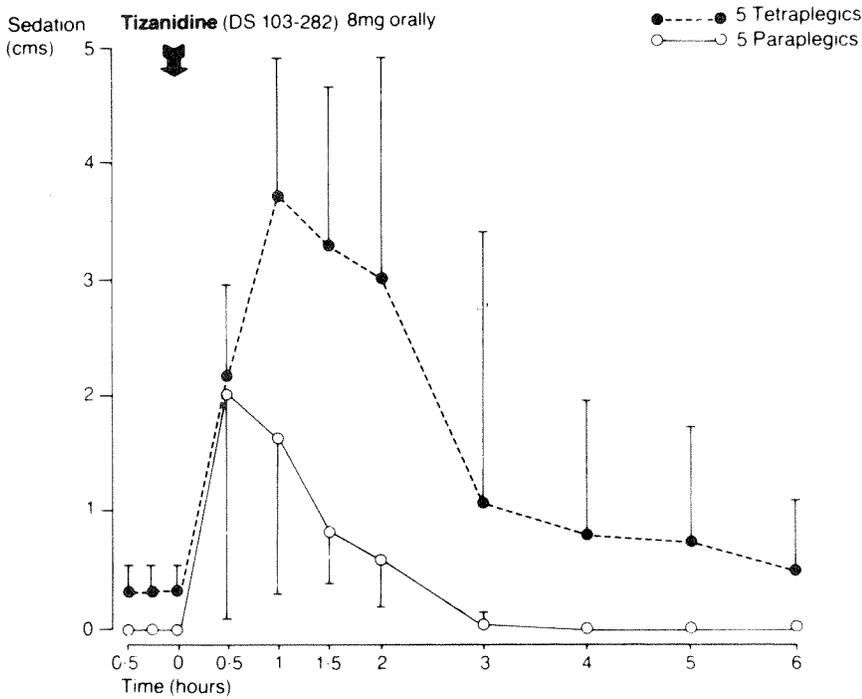


Figure 5. Sedation measured in centimeters (cms) on a 10 cm scale from the wide awake pole in tetraplegic and paraplegic patients before and after tizanidine given at time 0. Bars indicate means + SEM.

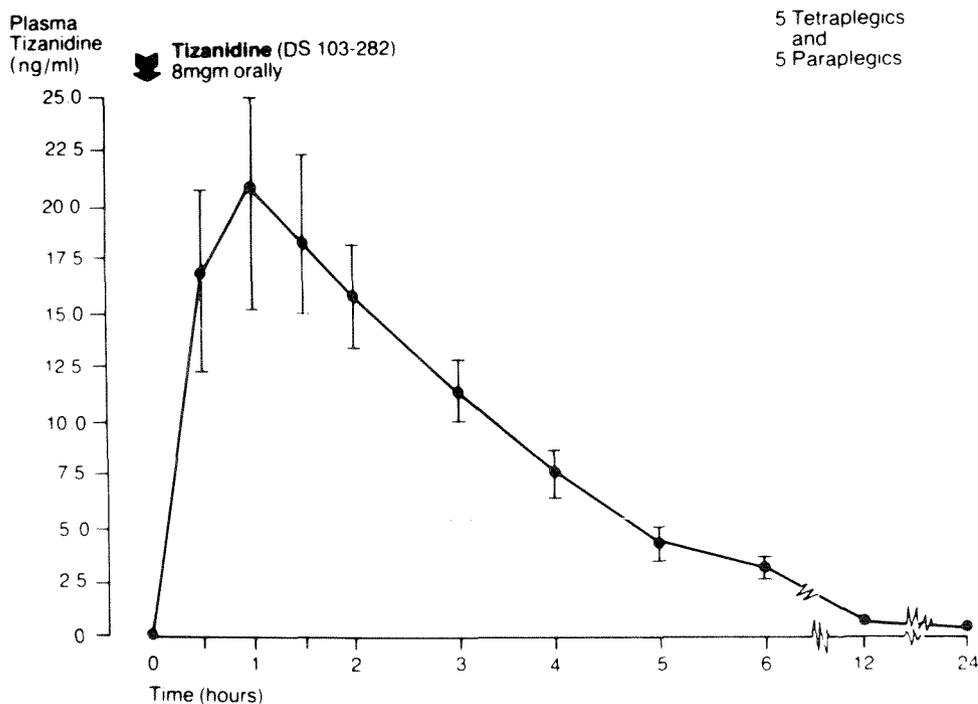


Figure 6.

Plasma tizanidine levels in 10 patients (5 tetraplegics and 5 paraplegics) before and for 24 hours after 8 mg oral tizanidine given at time 0. Bars indicate means + SD.

levels 12 and 24 hours after drug administration. The calculated plasma half-life was 2.7 ± 0.06 hours (Figure 6). Pharmacokinetic details are provided in Table 3.

Side effects

In the early part of the study, the only side effect that patients spontaneously acknowledged was sedation. Upon questioning, they admitted to a dry mouth. No other side effects were either reported or elicited.

Drug-free study

Measurements of spasticity, muscle power, blood pressure and heart rate on the drug-free day were not different from the pre-drug recordings when tizanidine was administered. There were no significant changes over the observation period.

DISCUSSION

The purpose of the study was to determine the efficacy and duration of the antispastic effects of a

single dose of tizanidine, to assess its side effects, and relate these effects to the pharmacokinetic profile of the drug. In tetraplegic and paraplegic patients, tizanidine had substantial antispastic effects. These effects were of rapid onset, which were consistent with its prompt absorption. The effects lasted for a period of between three to four hours. They were clearly noted in patients who had either been non-responsive to, or had side effects from, the antispastic drugs previously used. It was not the purpose of the study, nor was it possible, to make a direct comparison with other antispastic agents.

The reduction in spasticity occurred in the upper and lower limbs of the tetraplegics and the lower limbs of the paraplegics. In neither group was rebound spasticity observed, which was confirmed with formal testing 12 and 24 hours after administration of the drug. In the paraplegic patients there was no impairment of muscle power in the intact upper limbs: this is of great importance, because their mobility is dependent on activity in these muscles.

Clonidine, another imidazole derivative, lowers blood pressure in resting normotensive subjects.

Table 3.

The basic pharmacokinetic parameters in 10 patients with spinal cord injury. Peak plasma levels (CP) at time of maximum level (t/max) and area under the curve (AUC) together with elimination half-life (t 1/2 el) are indicated.

Patient	CP (ng/ml)	t/max (hours)	AUC (0-24 hrs) (ng/ml hours)	t 1/2 el (hours)
1	17.81	1	45.16	1.60
2	30.60	0.5	69.79	1.95
3	17.51	2	74.14	4.44
4	32.22	0.5	87.43	3.52
5	27.24	1	51.44	3.75
6	22.85	0.5	70.38	2.39
7	28.64	2	92.58	1.78
8	14.86	3	48.62	1.90
9	23.06	1	42.80	1.56
10	43.28	1.5	114.90	4.10
Mean	256.81	1.3	69.72	2.70
+ SD	+8.49	+0.8	+23.59	+1.13

This results from a central reduction in sympathetic nervous activity (8). In tetraplegics, clonidine has a minimal or no effect on resting supine blood pressure, but can reduce the elevated blood pressure (7) which results from reflex-isolated spinal sympathetic stimulation induced by urinary bladder stimulation (5,6). The initial blood pressure in our tetraplegics was higher than levels previously noted (2,5). This may have been dependent on reflex sympathetic stimulation secondary to increased muscle spasticity. Following tizanidine, there was a small but not significant fall in systolic blood pressure in both groups of patients, which would be consistent with a reduction in sympathetic activity either directly or indirectly through a reduction in muscle spasticity. There was no evidence of rebound hypertension. Heart rate fell in both groups of patients. The basal heart rate levels in the paraplegics were higher than in the tetraplegics; this may indicate that they have a greater sympathetic chronotropic drive as compared with the tetraplegics. The fall in heart rate after clonidine probably results from an increase in vagal tone; the levels fell significantly in both groups after tizanidine, and had

recovered in the paraplegics by the third hour, but remained lower in the tetraplegics for up to six hours.

After tizanidine there was an increase in sedation in both groups. This increased within half an hour after drug administration and had fallen by the third hour. By this time most patients were fully awake and not drowsy. The drug was easily tolerated, and the only other side effect elicited was dryness of the mouth.

The plasma levels of the drug were of relevance in relation to its pharmacodynamic effects. The drug was rapidly absorbed, with high levels reached within half an hour after administration and peak levels after the first hour. This was consistent with the observed maximal effects of tizanidine. The decline in levels of tizanidine was on a monoexponential basis, and the calculated half-life of the drug was 2.7 ± 0.06 hours. Levels were virtually undetectable 12 and 24 hours after drug administration. Methods aimed at reducing peak levels of the drug, but prolonging its action, may be of benefit.

We conclude that tizanidine was rapidly absorbed after oral administration and had antispastic effects in patients with spinal cord injuries suffering from moderate-to-severe degrees of spasticity. It had minimal effects on blood pressure, but lowered heart rate. It increased sedation and caused dryness of the mouth. It did not impair the muscle power of unaffected limbs in paraplegic subjects.

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