Pathophysiology of autonomic dysreflexia: long-term treatment with terazosin in adult and paediatric spinal cord injury patients manifesting recurrent dysreflexic episodes

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Introduction: Spinal cord injury (SCI) results in disruption of synaptic influences on the sympathetic preganglionic neurones. Remodelling of spinal cord circuits takes place in spinal neurones caudal to cord injury. There is an increased vascular alpha-adrenoceptor responsiveness, and peripheral afferent (bladder) stimulation in SCI subjects induces a marked noradrenaline spillover below the level of spinal lesion. These neurophysiological changes possibly contribute to the development of autonomic dysreflexia, a condition of sympathetic hyper-excitability that develops after cervical, or upper dorsal cord injury with resultant paroxysmal rise in arterial pressure, and provide the scientific basis for the use of terazosin, a once-a-day, selective alpha-one adrenergic blocking drug.

Objectives: The use of terazosin, a long-acting, alpha 1-selective blocking agent was investigated in SCI patients who developed recurrent symptoms of autonomic dysreflexia, eg headache, sweating flushing of the face together with an increase in the arterial pressure.

Design: An open, prospective study of the efficacy of terazosin in controlling recurrent autonomic dysreflexia in traumatic tetraplegic/paraplegic patients manifesting clinical features of dysreflexia in the absence of an acute precipitating cause such as a blocked catheter.

Setting: The initial assessment and treatment were carried out in the Spinal Injuries Centre. Subsequently, the patients were followed-up in the community. They were monitored by telephonic interviews, follow-up visits by the patients to the hospital, and home-visits by the staff of the spinal unit.

Subjects: Eighteen adults with tetraplegia (female: 1; male: 17), three children with ventilator-dependent tetraplegia and three adult male patients with paraplegia who exhibited recurrent features of autonomic dysreflexia in the absence of an acute predisposing factor for dysreflexia eg performance of an invasive procedure such as cystoscopy, digital evacuation of bowels, or acute urinary retention, were enrolled in this study.

Intervention: After discussion with the patients and their carers, terazosin was prescribed with a starting dose of 1 mg in an adult and 0.5 mg in a child administered nocte. The patients were observed for (1) drug-induced hypotension; (2) clinical symptoms due to side effects of terazosin; and (3) continued occurrence of dysreflexic symptoms. Step-wise increments of the dose of terazosin (1 mg in case of adults, and 0.5 mg in a child) was carried out at intervals of 3–4 days, if a patient continued to develop dysreflexia but did not manifest any serious side effect.

Outcome measures: Complete subsidence of dysreflexic symptoms, or development of an adverse event necessitating termination of the terazosin therapy was the clinical end point.

Results: The dysreflexic symptoms subsided completely with the terazosin therapy in all the patients. The twenty-one adult patients required a dose varying from 1–10 mg, whereas the paediatric patients required only 1–2 mg of terazosin. The side effects of postural hypotension and drowsiness were transient, and mild. One tetraplegic patient developed persistent dizziness and therefore, the drug therapy was discontinued.

Conclusion: In 21 adult and three paediatric spinal cord injury patients manifesting recurrent episodes of autonomic dysreflexia in the absence of an acute predisposing cause, the use of terazosin, a once-a-day, specific alpha-one blocker resulted in complete subsidence of the dysreflexic symptoms. However, one tetraplegic patient required termination of terazosin therapy because of persistent dizziness.

Keywords: terazosin; autonomic dysreflexia; spinal cord injury; tetraplegia; remodelling of spinal cord circuits

Introduction

Autonomic dysreflexia is an acute syndrome characterised by (1) a sudden increase in blood pressure with compensatory bradycardia, (2) headache, and (3) profuse sweating and vasodilation with skin flushing above the level of spinal cord injury. Autonomic dysreflexia occurs in patients with a spinal cord injury above the greater splanchnic outflow, usually above T-6; however, autonomic dysreflexia has been reported to occur with spinal cord injuries at neurological levels as low as T-8.¹ Proprioceptive and noxious stimuli below the level of injury may induce an episode of autonomic dysreflexia, and the acute increase in arterial blood pressure may cause seizures, intracerebral haemorrhage, or even death.² Although certain events such as distension of the urinary bladder or bowel, acute cystitis, cystoscopy, cystometry, percutaneous nephrolithotomy, extracorporeal shock wave lithotripsy and sexual act³ may precipitate autonomic dysreflexia, dyssynergic voiding and irritation of the trigone by an indwelling urinary catheter are the common causes for the occurrence of autonomic dysreflexia. An algorithm has been proposed for the management of an acute episode of autonomic dysreflexia after it has occurred.⁴ Sublingual administration of nifedipine, a calcium channel blocker, in a dose of ten milligrams secures rapid control of the sudden increase in blood pressure, and is the standard drug therapy for a spinal cord injury patient who has developed the clinical features of autonomic dysreflexia.

Some spinal cord injury patients tend to develop recurrent episodes of autonomic dysreflexia. In patients with a predilection for recurrent autonomic dysreflexia, it is desirable to prevent the occurrence of dysreflexic episodes. In this subgroup of tetraplegic and paraplegic subjects with a propensity towards recurrent episodes of autonomic dysreflexia, the precipitating cause for the occurrence of autonomic dysreflexia may elude precise identification in some. In others, dyssynergic voiding or an indwelling urinary catheter may be the underlying reason. But these patients may not find it easy to change their life style. Therefore, elimination of the precipitating cause for the occurrence of autonomic dysreflexia may not be feasible. Consequently, these special groups of spinal cord injury patients require round the clock protection against autonomic dysreflexia on a continual basis.

Spinal cord injury disrupts control of sympathetic preganglionic neurones (SPN) because bulbospinal input has been lost, and the remaining regulation is accomplished by spinal circuits consisting of dorsal root afferent and spinal interneurons.⁵ Experimental studies in rats have shown that soon after injury, there is temporary depression of cardiovascular function due to loss of bulbospinal excitatory input. Within a week of spinal cord injury, there is transient atrophy of SPN which could reinforce the sympathetic atonia and hypotension. There is also a loss of dendritic processes on preganglionic neurones, a condition that could render the neurones less receptive to excitatory input.

These changes may explain why patients do not manifest autonomic dysreflexia immediately after the spinal cord injury. In chronic spinal cord-injured rats, one month after cord transection, there is remodelling of the dendritic arbor of preganglionic neurones and the intensity of the reactive gliosis around the preganglionic neurones was diminished.⁶ By 30 days after complete transection, the atrophy of SPN had been reversed. This recovery of normal morphology in SPN, and reorganization of synaptic inputs to SPN are consistent with the return of large and sustained excitatory sympathetic responses that cause episodic hypertension (autonomic dysreflexia) after this time period. In clinical practice also, the episodic hypertensive responses associated with autonomic dysreflexia undergo a time-dependent increase in magnitude after cord injury.⁷ Moreover, sprouting of the central arbour of primary afferent neurones occur by 2 weeks after a spinal cord injury in rats.⁸ This exaggerated input to spinal interneurons in deeper laminae of the dorsal horn would also contribute to the development of autonomic dysreflexia. The current concepts on the neurophysiology of autonomic dysreflexia in experimental animals, and in spinal cord injury patients are summarised in Appendix 1.

These neurophysiological changes constitute the scientific foundation for the pharmacological treatment of recurrent autonomic dysreflexia with a selective alpha-1 adrenergic blocking agent. We report our clinical experience in 24 spinal cord injury patients who developed recurrent episodes of autonomic dysreflexia and were treated with terazosin, a once-a-day, selective alpha-1 adrenergic blocking drug.

Patients and methods

Patients with spinal cord injury who are registered with the Regional Spinal Injuries Centre, Southport were the source of subjects for this study. Any patient who recounted experiencing symptoms of autonomic dysreflexia, or who was detected to exhibit recurrent episodes of pounding headaches, sweating, or flushing of the face accompanied by an acute increase in the arterial blood pressure, was investigated further as to the possible existence of a predisposing factor for the occurrence of autonomic dysreflexia. Whenever an obvious precipitating factor for the happening of autonomic dysreflexia was detected, eg a blocked urinary catheter, appropriate treatment was instituted, *viz* insertion of a new urinary catheter in this patient. If performance of an invasive procedure was the predisposing factor for the occurrence of autonomic dysreflexia, an acceptable modification in the performance of such a procedure was adopted. For example, if digital evacuation of the bowels led to the occurrence of a dysreflexic episode, prior instillation of 2% lignocaine gel into the rectum was the appropriate treatment for the prevention of autonomic dysreflexia in that particular patient. However, there were situations when it was not possible to identify a predisposing factor for autonomic

dysreflexia. Rarely, in a patient developing recurrent episodes of autonomic dysreflexia, a change of his/her life style in order to prevent these dysreflexic episodes was not a viable option. In a female, C-4 tetraplegic patient irritation of the trigone by an indwelling urinary catheter was the probable cause for the occurrence of autonomic dysreflexia. It was not feasible to establish intermittent catheterisation regime, as self-catheterisation was impossible. She was on full time job and was leading an active social life which precluded urethral catheterisation five times a day by a carer. Therefore, she preferred to live with the indwelling urinary catheter, and take medication to prevent autonomic dysreflexia. Thus the criteria for inclusion in this prospective study were:

1. Patients with injury to the spinal cord who have been suffering from recurrent episodes of autonomic dysreflexia.
2. Failure to identify a specific predisposing factor for the occurrence autonomic dysreflexia in these patients manifesting recurrent dysreflexia symptoms, or
3. Difficulty in modifying the care plan of the patients in order to eliminate the predisposing factor for the occurrence of recurrent autonomic dysreflexic episodes.

Twenty-four patients who satisfied these criteria were the subjects of this report.

Treatment schedule with terazosin

The proposed treatment with terazosin was discussed with the patient and his/her carers. They were informed of the possible side effects of terazosin. If they agreed to the treatment with terazosin, their current medication list was checked. If a patient has been taking a thiazide diuretic say, for swelling of the feet, he or she was advised to stop the diuretic before commencing the treatment with terazosin, as an exaggerated first dose response (*vide infra*) has been identified in patients pre-treated with thiazide diuretics.⁹ An initial dose of either one mg in case of adults, or 0.5 mg in case of children, was administered once a day on retiring to bed. This special precaution of administering the first dose of terazosin at bedtime was observed as the first dose may cause collapse due to hypotensive effect within 30–90 min. Patients were warned to lie down if symptoms such as dizziness, or fatigue develop and to remain lying down until these symptoms abate completely.¹⁰ The carers were taught how to recognise the potentially serious adverse events to terazosin. The patients were encouraged to wear a thigh length elastic stocking hopefully to minimise the occurrence of postural hypotension and dizziness. The arterial blood pressure was measured daily as they were sitting up on a chair. Occurrence of the side effects due to terazosin, and symptoms of autonomic dysreflexia were recorded. If a patient continued to develop symptoms of autonomic

dysreflexia, and the side effects were either absent or only mild, the dose of terazosin was raised at intervals of 3–4 days, the dose increment being 1 milligram in case of adults, and 0.5 milligram in case of children. A maximum permissible dose of terazosin was set at 10 milligrams for an adult patient, and 2 milligrams for a child. The clinical end points were: (1) complete abatement of the symptoms and signs of autonomic dysreflexia; or (2) occurrence of major side effects which demanded discontinuation of drug therapy, or prevented any further increase in terazosin dosage in order to control the features of autonomic dysreflexia which were still present. After reaching the optimal dose of terazosin, the patients were reviewed either during their follow-up visits to the spinal injuries centre, or during the home visits made by the staff of the spinal injuries centre.

Results

The clinical details of these patients with spinal cord injury are given in Table 1. There were 18 adult tetraplegics (male: 17 and female: 1) and three male children with ventilator-dependent tetraplegia; there were three male paraplegic patients (level of lesion: T-4 in two patients and T-1 in one patient). No patient exhibited first dose reaction to terazosin. During terazosin therapy, the lowest blood pressure of 78/40 mmHg was recorded in a three year old boy who was getting 1 milligram of terazosin *nocte*. Among the adult tetraplegic subjects, the lowest recording of blood pressure was 85/50 mmHg in a 30 year old male tetraplegic patient with a neurological level of C-5. This patient was taking 2 milligrams of terazosin and he did not develop any side effect such as dizziness. A 39-year old tetraplegic patient has been taking 10 milligrams of terazosin to control the symptoms of autonomic dysreflexia. He did not develop any side effect to the 10 milligram dosage of terazosin. On one occasion, he was inadvertently given 45 milligrams of terazosin instead of 10 milligrams by his carer, as the new supply of terazosin tablets was of higher strength. He was admitted to the spinal injuries centre as a precautionary measure; he was given 50 grams of activated charcoal by mouth. He did not develop hypotension; his blood pressure remained around 123/70 mmHg. He was able to sit up without feeling dizzy the next afternoon, and was discharged home after 18 h of observation.

In contrast, a 54-year old tetraplegic patient (C-7) preferred to discontinue terazosin because he felt dizzy while he sat up. This tetraplegic patient required a dose of 6 milligrams of terazosin in order to abolish completely the symptoms of autonomic dysreflexia. His blood pressure recording while he was sitting on his chair was 80/52 mmHg. The side effects which were observed in other patients included (i) feelings of tiredness, and (ii) drowsiness; these side effects were mild, self-limiting, and were noticed only during the first week of treatment with terazosin. A 33 year old

Table 1 Clinical details of the patients who exhibited recurrent symptoms of autonomic dysreflexia and were treated with terazosin

<i>Patient initials</i>	<i>Sex</i>	<i>Year of birth</i>	<i>Year when he/she sustained spinal cord injury</i>	<i>Diagnosis</i>	<i>Type of urinary bladder drainage</i>	<i>Reasons for prescribing terazosin</i>	<i>Month & year when terazosin was started</i>	<i>Dose of terazosin</i>	<i>Blood pressure while taking terazosin (mmHg)</i>	<i>Side effects of terazosin</i>
WC	F	1965	1979	Trampoline accident Tetraplegia C-4	Indwelling urethral catheter drainage	Recurrent episodes of sweating, Headache	May 1997	3 mg nocte + oxybutynin 5 mg + 5 mg + 5 mg + 5 mg	90/60	nil
GN	M	1960	1985	Diving accident Tetraplegia C-5	Penile sheath drainage	Sweating and head ache during voiding	August 1996	5 mg nocte	92/63	nil
MH	M	1965	1986	Motor bike accident Tetraplegia C-5	Penile sheath drainage + intermittent urethral catheterisation	Recurrent episodes of headache	July 1997	3 mg nocte	117/76	nil
OC	M	1969	1995	Motor cycle accident Paraplegia T-4 Left brachial plexus injury	Penile sheath drainage	Recurrent episodes of headache	July 1997	8 mg nocte	123/83	nil
KW	M	1953	1968	Diving accident Tetraplegia C-4	Penile sheath drainage	Recurrent episodes of getting clammy	March 1997	6 mg nocte	114/59	nil
DM	M	1975	1992	Pedal cyclist – Hit & run accident Tetraplegia C-6	Penile sheath drainage	Recurrent episodes of banging head aches	September 1997	4 mg nocte	102/58	nil
GE	M	1967	1984	Diving accident Tetraplegia C-5	Indwelling urethral catheter drainage	Episodes of sweating, shooting pain in the head and rise in blood pressure (183/113 mmHg during one such episode)	April 1997	2 mg nocte	85/50	nil
SP	M	1971	1994	Water skiing accident Tetraplegia C-4	Indwelling urethral catheter drainage	Recurrent episodes of profuse sweating	June 1997	6 mg nocte	89/57	nil
CS	M	1989	1992	Pedestrian - knocked down by a car. C-1/C-2 dislocation. Ventilator-dependent tetraplegia	Indwelling urethral catheter drainage	Episodes of becoming extremely pale over the lip and face accompanied by a rise in blood pressure	December 1996	Terazosin 2 mg nocte + oxybutynin 5 mg + 2.5 mg + 5 mg	84/62	nil

Table continued

Table 1 continued

Patient initials	Sex	Year of birth	Year when he/she sustained spinal cord injury	Diagnosis	Type of urinary bladder drainage	Reasons for prescribing terazosin	Month & year when terazosin was started	Dose of terazosin	Blood pressure while taking terazosin (mm Hg)	Side effects of terazosin
SM	M	1994	1996	Ganglioglioma of the posterior fossa. Ventilator-dependent tetraplegia	Reflex voiding	Recurrent episodes of flushing, blotchy over face and rise in blood pressure to 153/100 mmHg	December 1996	Terazosin 1 mg nocte + oxybutynin 2.5 mg twice a day	78/40	nil
NB	M	1994	1995	Pedestrian knocked down by a car. Ventilator dependent tetraplegia	Intermittent catheterisation	Recurrent episodes of flushing with rise of blood pressure	May 1997	Terazosin 1 mg nocte + oxybutynin 2 mg four times a day	97/45	nil
TB	M	1954	1977	Diving accident. Tetraplegia C-6	Reflex voiding	Recurrent episodes of headache and sweating	September 1997	Terazosin 6 mg nocte	102/66	nil
SB	M	1968	1985	Motor bike accident Tetraplegia C-5	Reflex voiding + intermittent catheterisation 1–2 times a day	Recurrent episodes of flushing of the face	June 1997	Terazosin 5 mg nocte	106/63	nil
JW	M	1948	1992	Heavy pipe fell on his back whilst loading into a van Tetraplegia C-4	Penile sheath drainage	Recurrent episodes of very severe pain in the back of head; blotchiness all over the body	September 1996	Terazosin 4 mg nocte	100/50	nil
AM	M	1964	1978	Viral myelitis Paraplegia T-4	Penile sheath + Intermittent catheterisation	Recurrent episodes of headache with flushing of face when the blood pressure was recorded to be 180/110 mmHg	October 1997	Terazosin 3 mg	129/90	'I feel tired'
NF	M	1948	1972	Traumatic Paraplegia T-1	Penile sheath drainage	Recurrent episodes of flushing of the face	October 1997	Terazosin 2 mg	110/70	nil
OL	M	1968	1987	Hurt his neck while playing judo Tetraplegia C-3	Penile sheath drainage + intermittent catheterisation three times a day	Recurrent episodes of sweating and increase in blood pressure to 140/95 mmHg	November 1997	Terazosin 1 mg	90/60	nil

Table continued

Table 1 continued

<i>Patient initials</i>	<i>Sex</i>	<i>Year of birth</i>	<i>Year when he/she sustained spinal cord injury</i>	<i>Diagnosis</i>	<i>Type of urinary bladder drainage</i>	<i>Reasons for prescribing terazosin</i>	<i>Month & year when terazosin was started</i>	<i>Dose of terazosin</i>	<i>Blood pressure while taking terazosin (mm Hg)</i>	<i>Side effects of terazosin</i>
IG	M	1958	1985	Backseat passenger of a car which went out of control. Tetraplegia C-6	Intermittent catheterisation	Recurrent episodes of headache and sweating with rise in blood pressure to 180/110 mmHg especially during bowel emptying	October 1997	Terazosin 5 mg	110/60	nil
AG	M	1967	1984	Diving accident C-5 tetraplegia	Indwelling urethral catheter drainage	Recurrent episodes of headache while being turned	November 1997	Terazosin 4 mg	110/63	nil
RP	M	1943	1971	Motor cycle racing accident Tetraplegia C-7	Penile sheath drainage	Recurrent episodes of profuse sweating of the face	October 1997	Terazosin 6 mg	80/52	Discontinued the treatment with terazosin because of persistent dizziness
DB	M	1981	1996	Diving accident C-4 motor complete tetraplegia	Penile sheath drainage	Recurrent episodes of flushing of face and increase in blood pressure especially just before voiding	November 1997	Terazosin 2 mg	98/62	nil
AB	M	1959	1987	Road traffic accident C-6 tetraplegia	Penile sheath drainage	Recurrent episodes of sweating and headache accompanied by an increase of blood pressure to 194/105 mmHg	November 1997	Terazosin 10 mg	123/70	nil
PD	M	1970	1989	Road traffic accident - Front seat passenger C-4 complete tetraplegia	Indwelling urethral catheter drainage	Recurrent episodes of banging headache accompanied by a rise in blood pressure to 165/143 mmHg	December 1997	Terazosin 2 mg	96/58	nil
DD	M	1938	1970	Motorbike accident C-7 complete tetraplegia	Penile sheath drainage + intermittent catheterisation	Recurrent episodes of headache and sweating	January 1998	Terazosin 6 mg	110/48	nil

paraplegic patient (level of lesion: T-4) continued to experience tired feeling beyond the first week of drug therapy. However, this patient carried on taking terazosin and this side effect of feeling tired subsided spontaneously within a month of treatment. He has been taking 3 milligrams of terazosin *nocte* and has been feeling fine since then.

There was considerable variation in the dose of terazosin which was required for complete suppression of the symptoms and signs of autonomic dysreflexia. The 21 adult patients required doses varying from 1–10 milligrams, whereas the three paediatric patients needed a smaller dose of 1–2 milligrams (Table 1).

Discussion

Cardiovascular control becomes abnormal, and unstable after cervical and upper dorsal spinal cord injury, as there is either too little or, too much sympathetic activity. Too little sympathetic activity results in low blood pressure and postural hypotension. Too much sympathetic activity leads to autonomic dysreflexia. The mechanisms mediating autonomic dysreflexia are not due solely to disinhibition of the spinal reflexes, and to loss of descending bulbospinal inputs to spinal preganglionic neurones. Reorganization of synapses on spinal sympathetic neurones after cord transection may be crucial for the development of autonomic dysreflexia.¹¹ Understanding of the remodelling of spinal cord circuits, which occur after the decentralisation produced by the cord injury, is an essential prerequisite to devising therapeutic regimes either to limit the abnormal synaptic inputs to sympathetic preganglionic neurones which contribute to the occurrence of autonomic dysreflexia or to counter the peripheral effects of the excessive sympathetic activation.

As a peripheral afferent stimulation causes a marked increase in noradrenaline spillover below the level of lesion in SCI patients¹² and increased vascular alpha-adrenoceptor responsiveness has been demonstrated in tetraplegic patients,¹³ we treated these spinal cord injury patients who have been experiencing recurrent episodes of autonomic dysreflexia with a selective, alpha 1-adrenergic blocking drug. However, both NMDA (N-methyl-D-aspartate) and AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors contribute to spinal viscerosympathetic transmission and initiation of episodic hypertension in conscious spinal rats.¹⁴ Intrathecal administration of NMDA-receptor antagonist AP-5, and AMPA-receptor antagonist NBQX in rats relieve pain syndromes after spinal cord injury, effects that parallel the actions of those antagonists on reflex hypertension.¹⁵ Experimental studies in rats demonstrated that nerve fibres immunoreactive for the neurotransmitter amino acids, glutamate and GABA, provide most of the input to sympathetic preganglionic neurones caudal to a spinal cord transection.¹⁶ Synapses containing glutamate and GABA could

provide the anatomical substrate for the exaggerated sympathetic reflexes and the low sympathetic tone that result from spinal cord injury. Thus modulation of amino acid receptors in the spinal cord by continuous intrathecal administration of a selected drug may provide, yet another therapeutic method, for repressing autonomic dysreflexia. Indeed, in clinical practice, we observed complete disappearance of recurrent dysreflexic episodes in a tetraplegic patient following implantation of a programmable pump for continuous intrathecal infusion of baclofen, a GABA_B agonist.¹⁷

The mechanisms contributing to the exaggeration of spinal reflexes are acute loss of bulbospinal inhibition, and reactive reinnervation providing direct or indirect input from spinal and dorsal root afferent neurones to the partially deafferented SPN. As the latter process of reactive reinnervation increases with time after spinal cord injury,¹¹ it is logical to expect recurrent episodes of autonomic dysreflexia more frequently in the *chronic* spinal cord injury patients than in the *acutely* injured patients. In this clinical series of 24 patients, we observed a considerable time interval between the occurrence of spinal cord injury and their presentation with recurrent autonomic dysreflexic episodes. Although this time interval was more than 3 years in 19 of the 21 adult patients with spinal cord injury, the time lag was shorter in the three paediatric tetraplegic patients. (Table 1). It is not known whether the reorganization of synaptic inputs to SPN occurs more rapidly in children than in adults.

One of the patients who developed recurrent episodes of autonomic dysreflexia had T-4 paraplegia due to viral myelitis (see Table 1—patient AM). This case may indicate that a traumatic injury to the spinal cord is not necessary for the remodelling of spinal cord circuits. Thus autonomic dysreflexia may occur in patients with tetraplegic or paraplegia above T-6 level due to non-traumatic aetiology as well.

Chancellor and associates¹⁸ evaluated terazosin for the treatment of autonomic dysreflexia in 21 spinal cord injury men and found a significant improvement in the autonomic dysreflexia severity mean score (before: 2.9; after 3 months of treatment: 1.7) with no significant change in blood pressure. In their 21 men, the degree of head ache did not significantly improve with terazosin. Chancellor and associates¹⁸ however, did not elaborate upon either the selection of cases for treatment with terazosin, or the dosage adjustment in the individual patients. In the present study, all the 18 adult patients were completely relieved of their symptoms inclusive of head ache when the dose of terazosin was titrated according to their individual needs. Occurrence of headache as a symptom of autonomic dysreflexia, in our opinion, calls for immediate treatment by sublingual administration of the calcium channel blocker, nifedipine. It is important to recognise that terazosin therapy is not the first line of treatment for autonomic dysreflexia in spinal cord injury patients. If a tetraplegic patient gets dysreflexia when his urinary catheter is blocked, the

acute episode of dysreflexia should be treated with nifedipine administered sublingually. Further, appropriate modification(s) in the care plan should be implemented without delay to abolish the precipitating factor for the dysreflexic episodes. In the clinical situation cited above, future occurrence of dysreflexic episodes can be prevented by avoiding acute distension of the urinary bladder due to blocked catheter by changing the urinary catheter every 4 weeks instead of every 6 weeks. We do not recommend long-term terazosin therapy in such a patient in whom the precipitating cause can be identified, and suitable corrective strategies can be implemented to prevent the recurrence of the predisposing clinical situation. Thus, we reserve treatment with terazosin for the selected patients who manifest recurrent episodes of dysreflexia and in whom, it is not possible to identify the predisposing cause for the occurrence of autonomic dysreflexia, or in whom it is not feasible to abolish the precipitating factor for the dysreflexic episodes because of either social, or personal reasons.

Terazosin has been used more widely in patients with benign hyperplasia of prostate. The side effects of terazosin in the treatment of symptomatic benign prostatic hyperplasia were studied by analysis of seven prospectively designed placebo-controlled trials involving 3080 patients, 1689 of whom received terazosin in doses ranging from 1–20 mg daily for a total of 1282 patient-years of exposure. The most common side effects seen in patients treated with terazosin were dizziness (10.7%), asthenia (7.5%) and peripheral oedema (4.0%).¹⁹ The present study was carried out on 24 tetraplegic/paraplegic patients. Only one of these 24 patients developed a significant side effect of dizziness which required discontinuation of drug treatment. No other patient noticed any side effect which interfered with the daily activities of living. Of course, patients with spinal cord injury and patients with benign hyperplasia of prostate represent two different population groups and they are not comparable. However, rarity of the occurrence of side effects in the present study is possibly due to the fact that the terazosin doses were adjusted according to the needs of the individual patient. All the adult patients were started with a dose of 1 milligram and then the dose was raised in a graded manner depending upon the continued occurrence of dysreflexic symptoms, the increments being 1 milligram. We did not think that it was appropriate to prescribe a standard dose of say, 4 milligrams of terazosin to all adult patients with spinal cord injury exhibiting autonomic dysreflexia. By starting with a dose of 1 milligram in adults, and 0.5 milligram of terazosin in case of children and then gradually building up the dose over a period of time, probably the body system was able to adopt itself to the pharmacological actions of terazosin, especially the hypotensive effect of this selective alpha-1 adrenergic blocking drug. Further, by tailoring the terazosin dosage to the individual patients requirements as indicated by the continued presence of dysreflexic

symptoms, we found that patients with spinal cord injury required a varying dose of terazosin, the range being 1–10 milligrams. Further, we took precautions to reduce the occurrence of postural hypotension right from the beginning of terazosin therapy. All the patients were advised to wear elastic stockings (thigh length) to prevent pooling of blood in the lower limbs; some tetraplegic patients wore abdominal binders as well. All the patients received terazosin in the late evening after they were put to bed. There is some evidence that bed-time dosing of alpha-blockers tend to reduce the asthenia and dizziness.²⁰ Adverse events to terazosin were significantly decreased by administering the drug in the evening to normotensive men with symptomatic prostatism.²¹

McKiernan and Lowe¹⁹ observed a statistically significant decreased risk of urinary tract infection and myocardial infarction in the terazosin-treated group among patients with benign hypertrophy of prostate. The finding of a decreased incidence of myocardial infarction in the terazosin group may be attributable to the simultaneous favourable effects of terazosin on blood pressure, serum lipids, and left ventricular hypertrophy.^{22,23}

The proven benefits of terazosin to individuals with benign prostate hypertrophy cannot be extrapolated to patients with spinal cord injury as these represent two distinct populations. However, terazosin therapy results in improved voiding with a decreased residual urine in spinal cord injury patients as well. Holding large amount of residual urine is one of the predisposing factors for the occurrence of urinary tract infection in tetraplegic and paraplegic patients. Improved bladder emptying along with a decrease in the amount of residual urine as a consequence of terazosin therapy is likely to result in a diminished incidence in urinary infection in spinal cord injury patients taking terazosin on a long-term basis.

Further, spinal cord injury patients with autonomic dysfunction are reported to have an increased risk for cardiovascular morbidity and mortality.²⁴ Cardiovascular diseases are the most frequent cause of death among persons with spinal cord injury, and these diseases are reported to occur prematurely in the disabled compared to the able-bodied population.²⁵ If terazosin therapy results in favourable changes in the lipid profile of patients with spinal cord injury, such a drug-induced decrease in the blood cholesterol level may be yet another advantage of terazosin therapy in the spinal cord injury patients. However, these hypotheses on the effects of terazosin, *viz* (i) decreasing the incidence of urinary infection and (ii) diminishing the morbidity due to cardiovascular diseases in patients with spinal cord injury, need to be tested by carrying out controlled clinical trials in the spinal cord injury population.

With improved understanding of the neurobiology of the traumatised spinal cord, a molecular biological approach may become feasible in future, for the modulation of the remodelling processes occurring in

the spinal cord caudal to the level of injury, as sprouting of primary afferent neurones and spinal interneurons with formation of new synapses on spinal preganglionic neurones may be crucial for the development of autonomic dysreflexia. With the molecular cloning of the receptors for excitatory neurotransmitters, and application of antisense oligonucleotides technology, it may be possible to block or alter the expression of the genes for the specific excitatory receptor subtypes.²⁶ Therefore, in the next century, therapeutic interventions may be directed at the genes themselves, in an attempt to treat disorders that involve the exaggerated sympathetic reflexes, such as autonomic dysreflexia.

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Appendix 1 Neurophysiology of autonomic dysreflexia following spinal cord injury

I *Changes in sympathetic preganglionic neurons (SPN)*

- 1 Disruption of descending bulbospinal input to SPN leads to partial deafferentation.
- 2 Initial, transient atrophy of sympathetic preganglionic neurones within 7 days of cord transection or hemisection.⁶
- 3 Loss of dendritic processes on preganglionic neurones renders the SPN less receptive to excitatory input.
- 4 Within 30 days of cord injury, the preganglionic neurones have reestablished a normal dendritic arbor. This recovery of morphology heralds the advent of autonomic dysreflexia which signals the development of abnormal synaptic connections within the spinal cord.
- 5 The preganglionic neurones may express new receptors, or up-regulate normally expressed receptors in response to their initial deafferentation.²⁷

II *Neurobiochemical changes in the spinal cord caudal to cord injury*

- 1 Increases in expression of synaptophysin, a phosphoprotein found in synaptic vesicles in axon terminals, and a marker of synaptogenesis, caudal to the cord transection is consistent with an increase in synaptic terminals in the grey matter, and suggests possible sprouting of local axons of interneurons which signals new inputs to the SPNs that mediate the sympathetic hyper-responsiveness of established autonomic dysreflexia.^{6,28}
- 2 In chronic spinal rats, the catecholamine-synthesizing enzyme, dopamine beta-hydroxylase expression was up-regulated in somata within the intermediate gray matter of spinal segments caudal to the transection. The numbers of somata immunoreactive for this enzyme increased sixfold by 14 days after cord transection, compared to the few somata counted in control rats.⁵ The presence of dopamine beta-hydroxylase in a markedly greater number of neuronal somata after cord transection reflects significant up-regulation of gene expression for this enzyme, possibly indicating a switch by these neurones to an adrenergic phenotype.
- 3 There is an increased expression of substance P, and more wider distribution of substance P, immunoreactive fibres caudal to cord transection.⁵ The increased area of substance P-immunoreactive fibres may be due to an increase in synthesis of this peptide in spinal interneurons, or to sprouting of dorsal root afferents or spinal interneurons that contain substance P. As the effects of substance P on spinal preganglionic neurones can be excitatory, a spinal source of

substance P could contribute to the development of autonomic dysreflexia.

- 4 An increased central arbour of calcitonin gene-related peptide containing primary afferent fibres suggests sprouting of unmyelinated afferent fibres and upregulation of their excitatory neuropeptide expressions.⁸

III *Remodelling of spinal cord circuits after spinal cord injury*

- 1 Following the initial retraction of the dendritic tree of the SPN, there is regrowth.
- 2 Partial deafferentation of sympathetic preganglionic neurones after spinal cord transection stimulates sprouting of myelinated and unmyelinated primary afferent fibres, and possibly interneurons. Afferent fibre sprouting did not reach autonomic or motor neurones directly but may cause hyper-reflexia by increasing inputs to interneurons.⁸
- 3 The combination of loss of descending pathways to the SPN and formation of new synaptic inputs which are inappropriate because of their density or their source, leads to the development of exaggerated reflex responses, and abnormal cardiovascular control.

IV *Hypersensitivity of vascular alpha-adrenoceptors in tetraplegic patients*

In tetraplegic patients with a history of autonomic dysreflexia, there was an increased responsiveness of venous alpha-adrenoceptors to locally infused noradrenaline in the foot vein as shown by a significant shift to the left of the dose-response curve. The results were similar in all patients, and were in marked contrast to those obtained in age-similar normal subjects who required a 6–7-fold increase in noradrenaline concentration to produce a comparable 50% venoconstriction.¹³ These observations suggested that the hyper-responsiveness of alpha-adrenoceptors which were observed in veins may also be present in arteries, and the hypersensitivity of vascular alpha-adrenoceptors may be important in the manifestation of autonomic dysreflexia in patients with tetraplegia.

V *Peripheral afferent stimulation causes marked noradrenaline spillover below lesion level in SCI patients*

Peripheral afferent (bladder) stimulation below the level of lesion in SCI subjects gave rise to 15-fold increase in leg noradrenaline spillover from a basal value of 0.06 pmol/min/100 g to 0.91 pmol/min/100 g. Such a marked increase in the amount of noradrenaline spillover suggests that the amount of transmitter released per nerve impulse may be augmented caudal to level of spinal cord injury.¹²