Research Paper

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A study of the alpha-1 adrenoceptor blocker prazosin in the prophylactic management of autonomic dysreflexia in high spinal cord injury patients

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THE ability of the alpha-1 adrenoceptor antagonist, prazosin, to reduce the severity and duration of episodes of autonomic dysreflexia was studied in cervical and high thoracic spinal cord injury patients with documented episodes of autonomic dysreflexia. Sixteen patients participated in a double blind parallel group study comparing prazosin 3 mg b.d. with placebo given for 2 weeks. Both groups were matched for age, sex and baseline severity of autonomic dysreflexia episodes. Prazosin was well tolerated and did not produce a significant lowering of resting blood pressure. Compared to baseline measurements, patients allocated to prazosin therapy were found to have fewer severe episodes of autonomic dysreflexia and during these episodes to have significant reductions in average rise in systolic and diastolic blood pressure, symptom duration and requirement for acute antihypertensive medication. The severity of headache during individual autonomic dysreflexia episodes was also diminished with prazosin therapy. No symptom parameter was significantly altered by placebo therapy. It is concluded that prazosin is superior to placebo in the prophylactic management of autonomic dysreflexia and that these findings are consistent with suggestions that alpha-1 adrenoceptors play an important role in the pathogenesis of this syndrome.

Key words: Autonomic dysreflexia, Blood pressure, Tetraplegia, Prazosin, Alpha adrenoceptor

Introduction

Autonomic dysreflexia is a syndrome characterized by profound pressor responses, sweating, headache and other symptoms occurring in cervical or high thoracic patients injury in response to sensory stimuli below the level of cord damage.[1] While the pathogenesis of autonomic dysreflexia is uncertain, one possibility is that spinal sympathetic reflexes mediated via the decentralized cord are amplified because of a loss of descending inhibitory pathways and because of supersensitivity of vascular alpha adrenoceptors resulting from chronic low levels of basal sympathetic stimulation.

Resting daytime plasma noradrenaline levels and spillover rates are lower in tetraplegic patients than neurologically intact subjects.[2] In addition, chronic spinal cord injury patients have enhanced blood pressure rises in response to exogenous infusion of catecholamines[3,4] and angiotensin II[4] which has been interpreted as reflecting both altered baroreceptor sensitivity[5] and increased vascular reactivity to both alpha-1 and alpha-2 adrenoceptor agonists and to angiotensin II.[4] Baroreceptor reflexes (which tend to suppress rises in blood pressure during infusions of pressor substances) were less variable in tetraplegic patients than controls.[4]

These observations have not allowed ready separation of the relative importance of changes in baroreceptor sensitivity and altered vascular sensitivity to alpha-1 and alpha-2 adrenoceptor agonists in mediating the pressor effects and symptoms of the syndrome of autonomic dysreflexia. To examine further the role of vascular alpha-1 adrenoceptors in autonomic dysreflexia and to assess the value of alpha-1 adrenoceptor blockade as therapy, we studied the efficacy of the highly specific alpha-1 adrenoceptor antagonist, prazosin, as prophylactic treatment for autonomic dysreflexia.

Methods

Subjects: Sixteen consecutive spinal cord injury patients aged 18 to 60, with transection levels at T6 or above and who were at least 3 months post-injury were investigated. All patients had had at least two episodes of symptomatic autonomic dysreflexia in the preceding 7 days. During these episodes, full documentation was obtained by specially instructed and trained Spinal Unit nursing staff on duration of symptoms, maximum rise in blood pressure and requirement for acute pharmacological intervention. Symptom severity was assessed by the patient according to a semiquantitative scale (0 = nil, 1 = mild, 2 = moderate, 3 = severe) and recorded during each episode. For the purposes of the study, autonomic dysreflexia

was strictly defined as a rise above baseline in systolic blood pressure greater than 30 mmHg or diastolic blood pressure of greater than 20 mmHg (manual sphygmomanometer readings), with at least one associated symptom consisting of either sweating, flushing, headache, muscle spasm or cutis anserina (goose flesh). The patients were not taking drugs known to affect sympathetic nervous system function. Fully informed consent was obtained from all subjects and the protocol was approved by the Austin Hospital Ethical Review Committee.

Blood pressure measurement: Manual sphygmomanometer recording of blood pressure was performed by specially trained Spinal Unit Nursing Staff. Episodes of autonomic dysreflexia were confirmed by the Nursing Staff in response to the patient notifying them of the commencement of symptoms. Blood pressure was then measured each minute for 10 min, then every 5 min for 30 min then every 10 min until all symptoms had disappeared and blood pressure had returned to baseline levels. The total time for each episode varied from 2.5 min to 2 h, but most episodes lasted 30 min or less. Blood pressure levels were also recorded 4 h throughout the 2 weeks of the study. Blood pressure was measured in the sitting position during waking hours and in the supine position at night. Baseline blood pressure was defined as the measurement taken prior to the commencement of the documented autonomic dysreflexia episode.

Study design: The patients were randomly allocated to receive either oral prazosin 3 mg b.d. or matching placebo for a 2 week period. Study medications were dispensed by the Hospital's Pharmacy Department, with the investigators remaining blinded to drug allocation for the duration of the study. Patients were commenced on 1 mg b.d. for the first 24 h, the first dose being administered at night when the patient was in bed. The dose was then increased to 3 mg b.d. for the remainder of the 2 week period. The initial low dose was given to avoid first dose postural hypotension and the dose of 3 mg b.d. had been found in a pilot study not to cause significant recumbent or sitting hypotension in spinal cord injury patients.

If an episode of autonomic dysreflexia occurred during the 2 week study period this was documented by the Nursing Staff by blood pressure measurement as described for the prestudy period. They also carefully recorded the nature and duration of symptoms. The patients kept a personal diary and noted maximal symptom severity during each episode, having been instructed by the investigators in the assessment of symptoms according to the semiquantitative scale used in the study. The nursing staff also recorded any interventions required to end an episode. If at any stage during an autonomic dysreflexia episode the blood pressure reached a level of 105 diastolic or 180 systolic, acute antihypertensive treatment (sublingual nifedipine 10 mg capsule) was instituted.

For the purposes of the study, only episodes of autonomic dysreflexia occurring beyond day 3 of the 2 week period of therapy were included in the analysis. The analysis was designed in this manner in order to permit blood levels of prazosin to reach steady state following the increase from initial dose (1 mg b.d. over the first 24 h) to maintenance (3 mg b.d.).

Statistical analysis: The mean and standard deviation of parametrically distributed variables i.e., age, time since spinal cord injury, resting blood pressure levels, rise in systolic and diastolic blood pressure and duration of symptoms were calculated in both the active and placebo group and measured before and after 2 weeks of therapy. These data were analysed by two-way analysis of variance with pairwise comparisons by analysis of simple effects. For the purposes of statistical analysis, if no episodes of autonomic dysreflexia occurred in a patient during the study period, the rise in blood pressure and duration of symptoms was allocated as zero to that patient. Non-parametric variables were analysed using the Kruskal–Wallis test (individual symptoms) and the Fischer's exact test (requirement for acute pharmacological intervention, number of subjects with severe symptoms). The latter statistical test was required to be performed because of the small number of patients evaluated for these parameters.

Results

Patients allocated to placebo and prazosin groups were similar with respect to demographic data. One patient was withdrawn from the analysis after the study was unblinded because he had undergone a major urological procedure during the 2 week period of therapy. There were no significant differences between the two study groups with respect to age range of spinal patients (placebo, mean 31.8 years, prazosin, mean 30.5 years, $p = 0.45$), sex (placebo, seven male, no female; prazosin, seven male, one female), time since spinal cord injury (placebo, 4.7 ± 3.6 years [mean $\pm$ standard deviation]; prazosin, 3.2 ± 2.7 years, $p = 0.32$) or cigarette smoking (two patients in each group). The causes underlying episodes of autonomic dysreflexia in these patients are documented in Table 1.

Mean ($\pm$standard deviation) of baseline systolic and diastolic blood pressure levels together with systolic and diastolic blood pressure rise during

Table 1. Causes of autonomic dysreflexia

	Placebo group	Prazosin group
Unable to be determined	2	4
Urinary tract infection	2	1
Detrusor–sphincter–dyssinergia	1	1
Post-sphincterotomy	1	0
Post-insertion penile prosthesis	0	1
Post-haemorrhoidectomy	0	1
Muscle spasticity	1	0

autonomic dysreflexia episodes are displayed in the two study groups before commencement of therapy and after 2 weeks of therapy in Figs 1 and 2. Baseline systolic blood pressure levels were not altered significantly by 2 weeks of either prazosin therapy or placebo. There were no significant differences in levels of systolic or diastolic blood pressure between the two therapies after 2 weeks treatment or in the extent of systolic blood pressure rises during autonomic dysreflexia episodes before commencement of therapy. The rise in systolic blood pressure during episodes of autonomic dysreflexia was however significantly reduced during therapy with prazosin but not placebo ($p = 0.010$, $p = 0.914$ respectively) and the rise in systolic blood pressure during episodes of autonomic dysreflexia in the prazosin group was significantly lower than in the placebo group

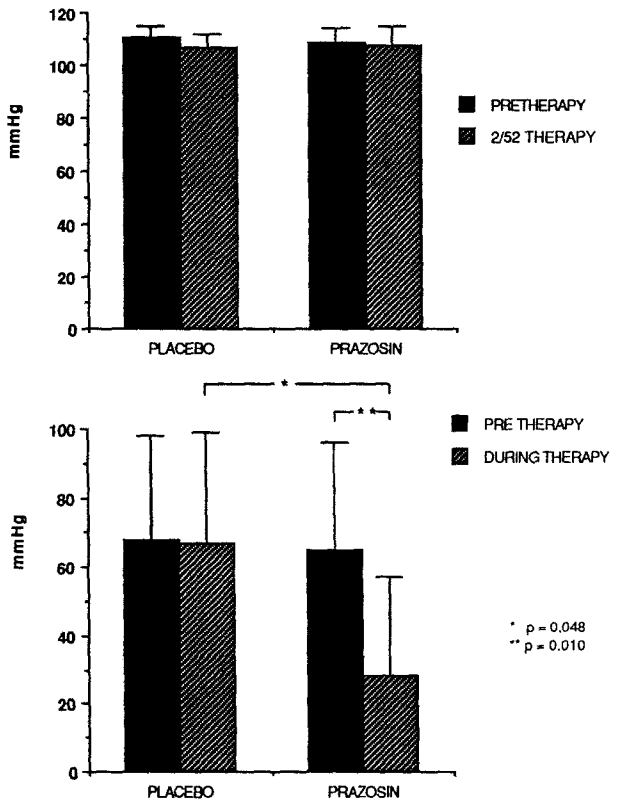

FIG. 1. Mean (± standard deviation) of baseline systolic blood pressure levels (upper panel) together with systolic blood pressure rise during autonomic dysreflexia episodes (lower panel) are displayed in the two study groups before commencement of therapy and after 2 weeks of therapy. Baseline systolic blood pressure levels were not significantly altered by 2 weeks of either prazosin therapy or placebo ($p = 0.39$, $p = 0.21$ respectively). There were no significant differences in levels of systolic blood pressure between the two therapies after 2 weeks treatment ($p = 0.81$). There were no significant differences between the two groups in extent of systolic blood pressure rises during autonomic dysreflexia episodes before commencement of therapy ($p = 0.848$). The rise in systolic blood pressure during episodes of autonomic dysreflexia was significantly reduced during therapy with prazosin but not placebo ($p = 0.010$**, $p = 0.914$ respectively) in comparison to rises occurring prior to commencement of therapy. There was a significant reduction in systolic blood pressure rise during therapy with prazosin in comparison to placebo ($p = 0.048$*).

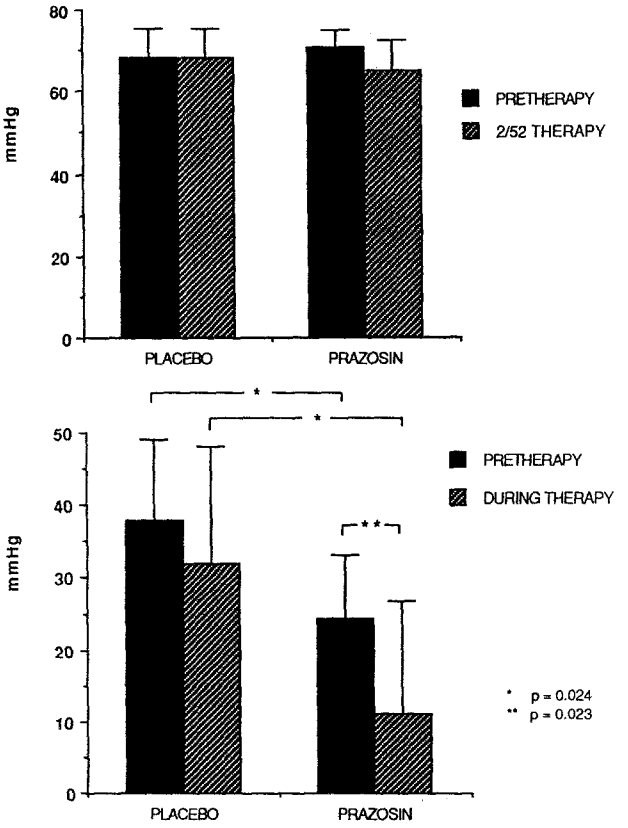

FIG. 2. Mean (± standard deviation) of baseline diastolic blood pressure levels (upper panel) together with diastolic blood pressure rise during autonomic dysreflexia episodes (lower panel) are displayed in the two study groups before commencement of therapy and after 2 weeks of therapy. Baseline diastolic blood pressure levels were not significantly altered by 2 weeks of either prazosin therapy or placebo ($p = 0.061$, $p = 1.0$ respectively). There were no significant differences in levels of diastolic blood pressure between the two therapies after 2 weeks treatment ($p = 0.09$). The extent of diastolic blood pressure rises during autonomic dysreflexia episodes before commencement of therapy was significantly greater in the placebo than the prazosin group ($p = 0.024$*). The rise in diastolic blood pressure during episodes of autonomic dysreflexia was significantly reduced during therapy with prazosin but not placebo ($p = 0.023$**, $p = 0.318$ respectively) in comparison to rises occurring prior to commencement of therapy. There was a significant reduction in diastolic blood pressure rise during therapy with prazosin in comparison to placebo ($p = 0.024$*).

($p = 0.048$). Diastolic blood pressure rises during autonomic dysreflexia episodes before commencement of therapy were significantly greater in the placebo than the prazosin group ($p = 0.024$). However the rise in diastolic blood pressure during episodes of autonomic dysreflexia was significantly reduced during therapy with prazosin but not placebo ($p = 0.023$, $p = 0.318$ respectively) and the rise in diastolic blood pressure during episodes of autonomic dysreflexia in the prazosin group was significantly lower than in the placebo group ($p = 0.024$).

Mean symptom duration during autonomic dysreflexia episodes (±standard deviation) in the two study groups before commencement of therapy and during therapy are presented in Fig. 3. There were no significant differences between the two groups in symptom duration during autonomic dysreflexia episodes before commencement of therapy. However symptom duration during episodes of autonomic dysreflexia was significantly reduced during therapy with prazosin but not placebo ($p = 0.013$, $p = 0.917$ respectively).

Rise in blood pressure and symptom duration during autonomic dysreflexia episodes were also measured during the first 2 days of therapy, although not included in the formal analysis of therapeutic efficacy as full dose steady state was only reached on day 3. Systolic blood pressure rise was significantly reduced in the prazosin group in comparison to placebo ($p = 0.02$) during the first 2 days of therapy (but not diastolic blood pressure rise or symptom duration).

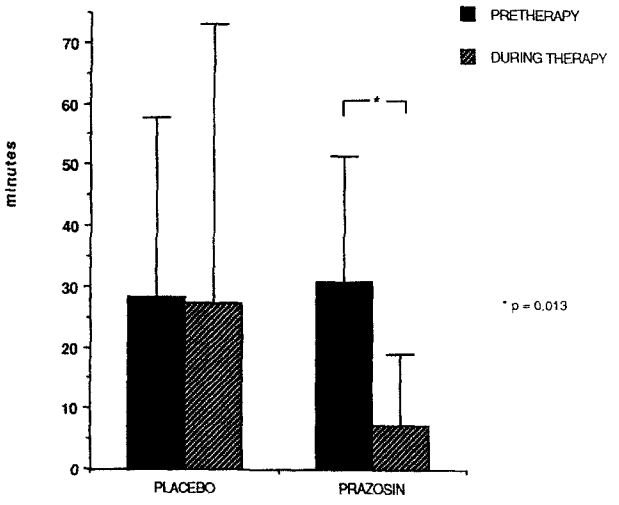

FIG. 3. Mean symptom duration during autonomic dysreflexia episodes (± standard deviation) in the two study groups before commencement of therapy and during therapy. There were no significant differences between the two groups in symptom duration during autonomic dysreflexia episodes before commencement of therapy ($p \approx 0.841$). Symptom duration during episodes of autonomic dysreflexia was significantly reduced during therapy with prazosin but not placebo ($p = 0.013$**, $p = 0.917$ respectively) in comparison to symptom duration prior to commencement of therapy. There were no significant differences in symptom duration during therapy in the two treatment groups ($p = 0.25$).

No subjects in the placebo group became completely free of symptomatic episodes of autonomic dysreflexia during the 2 week study period (days 3–14), whereas this occurred with four of the eight subjects in the prazosin group. This meant that during the treatment period in the prazosin group four subjects had nine autonomic dysreflexia episodes in comparison to placebo (seven subjects, eleven episodes). However, as documented in Table 2, symptoms during prazosin therapy (but not placebo) were reduced considerably in intensity. The severity of headache was significantly reduced in patients receiving prazosin but not placebo therapy ($p = 0.048$, $p = 0.708$ respectively) and headache severity during prazosin therapy was significantly less than placebo ($p = 0.021$). By contrast, there were no significant changes in sweating severity either in the prazosin ($p = 0.10$) or the placebo ($p = 0.47$) groups in the treatment phase nor in flushing and/or the appearance of a rash and other symptoms (muscle spasm, cutis anserina) during prazosin ($p = 0.30$, 0.23 respectively) or placebo ($p = 0.60$, 0.82) treatment. However, when relatively severe symptoms (i.e., symptom grading of greater than 1) only were analysed, these relatively severe symptoms were found to be significantly reduced in all symptom groups following prazosin therapy, but only for flushing/rash in those receiving placebo.

Fifty per cent of the prazosin group and 43% of the placebo group required sublingual nifedipine prior to commencement of therapy. No patient in the prazosin group required sublingual nifedipine following commencement of therapy ($p < 0.001$) whilst three of seven patients in the placebo group required sublingual nifedipine following commencement of therapy.

Patients experienced very few medication-related side effects during the course of the study. The only symptom attributable to therapy occurred in one patient who complained of significant postural hypotension during the study period. Following unblinding at the completion of the study, this patient was found to have been receiving placebo. There were no other drug related adverse events.

Discussion

One of the major problems in the assessment of prophylactic management of autonomic dysreflexia is the tendency for the episodes to become less severe and disappear over a period of weeks to months. The present study overcame this problem by utilizing a placebo controlled parallel group design in order to assess the efficacy of proposed treatment and has demonstrated that therapy with the alpha-1 adrenoceptor antagonist prazosin is superior to placebo for the prophylactic treatment

Table 2. Individual data on symptom severity, as determined by semiquantitative patient assessment, during episodes of autonomic dysreflexia that met the entry criteria to the study (two episodes of significant blood pressure elevation above baseline and at least one typical symptom within the previous 7 days) and during therapy in the two study groups

Patient number	Symptom severity								Number of relatively severe AD episodes***
	On entry				During study				
	Sweating	Headache	Flushing/ rash	Other*	Sweating	Headache	Flushing/ rash	Other*	
Placebo									
1	2	0	2	0	1	0	1	0	1
2	0	0	3	0	0	0	1.5	0	3
3	3	0	0.5	1	3	0	0	0	1
4	1.5	2	1.5	0	3	3	2	0	1
5	0.5	2.5	0	0	2	2	0	0	1
6	0	0	0	3	1	0	0	3	1
7	1	2	2	1	1	2	2.5	3	3
*n***	3	3	3	1	3	3	3	2	9
Prazosin									
1	0	0	2	2.5	0	0	0	0	0
2	1.5	3	0	0	0	0	0	0	0
3	0	0	0	1.5	0	0	0	1.5	1
4	2	2	0	0	0	0	0	0	0
5	1	3	1	0	0	0	0	0	0
6	0.5	2.5	1	0	1	1	1	0	1
7	0.5	1	0	0	0.5	1.7	0.5	0	1
8	2.5	1	2.5	0	1	0.5	0.5	0	1
*n***	3	3	2	2	0	1	0	1	4

* muscle spasm, cutis anserina. ** n = number of patients with relatively severe (grading > 1) symptoms.
*** number of autonomic dysreflexia (AD) episodes with relatively severe (grading > 1) symptoms occurring during the 2 week study period.

of autonomic dysreflexia in chronic spinal cord injury patients. Furthermore, prazosin was at least as well tolerated as placebo and did not lead to significant falls in resting supine or sitting blood pressures. This represents the first study to demonstrate, in a placebo controlled, double blind manner, the efficacy of prophylactic drug therapy for this condition.

Significant improvements were demonstrated in a wide number of parameters of autonomic dysreflexia severity following therapy with prazosin but not placebo. These parameters included extent of systolic and diastolic blood pressure rise, duration of symptoms and number of relatively severe symptoms occurring during an autonomic dysreflexia episode.

It is most likely that the beneficial effects of prazosin in the prophylactic treatment of autonomic dysreflexia result from the blockade of vascular alpha-1 adrenoceptors, which are activated by augmented spinal sympathetic reflexes.[6]

Alpha-1 adrenoceptor blockade with prazosin (at doses lower than those used in this study) has been demonstrated to shift the dose–response curve to infusion of the alpha-1 adrenoceptor agonist phenylephrine to the right in normal subjects.[7] While the effect of prazosin on phenylephrine dose–response curves have not as yet been studied in spinal patients, similar or perhaps greater effects of prazosin may be expected as spinal patients are more sensitive to the pressor effects of phenylephrine than normal persons.[4] The present findings also support the suggestion that increased vascular alpha-1 adrenoceptor sensitivity plays a pathogenetic role in the aetiology of this syndrome.

It is also possible that the beneficial effects observed with prazosin in autonomic dysreflexia may have derived, at least in part from the effect of alpha adrenoceptor blockade on improving bladder emptying. The physiological internal sphincter and the bladder neck may respond to alpha adrenergic blockade, as previously demonstrated with phenoxybenzamine in neurogenic bladder dysfunction.[8,9] In addition, detrusor–sphincter–dyssinergia[10] (detrusor muscle contracting against a closed external urethral sphincter), a common condition in quadriplegia, often results in marked elevations in bladder pressure with associated AH episodes. The external urethral sphincter (unlike the internal sphincter) is poorly innervated by efferent autonomic pathways[11] and prazosin would thus not be expected to directly improve opening of the external sphincter during detrusor contraction. However, there is some evidence to suggest a role for prazosin acting on the external sphincter via a central mechanism.[12] As urodynamics were not performed in these patients, we cannot fully exclude the possibility that improvements in urodynamic parameters may have occurred in the prazosin group and contributed to the beneficial effects of prazosin. However, as very few patients were found to have

impaired bladder emptying or detrusor–sphincter–dyssinergia as the cause of the autonomic dysreflexia in this study (Table 1), it would appear unlikely that the beneficial effects observed with prazosin in automic hyperreflexia would be due primarily to its actions on the bladder or urethra.

Detrusor–sphincter–dyssinergia[8] (detrusor muscle contracting against a closed external urethral sphincter), a common condition in high spinal cord lesions, which often results in marked elevations in bladder pressure with associated autonomic dysreflexia episodes. The external urethral sphincter is poorly innervated by efferent autonomic pathways[9] and prazosin would thus not be expected to directly improve opening of the external sphincter during detrusor contraction. There is evidence that prazosin may act on the external sphincter via a central mechanism[10] but this is less likely to have played a prominent role. A physiological internal sphincter of the bladder neck or proximal insertion may respond to alpha-adrenergic blockade, as previously demonstrated with phenoxybenzamine in neurogenic bladder dysfunction.[11,12] As urodynamics were not performed in these patients, we cannot therefore fully exclude the possibility that improvements in urodynamic parameters may have occurred in the prazosin group and contributed to the beneficial effects of prazosin.

The benefits observed during prazosin therapy appeared to be mainly due to attenuation of blood pressure rises and duration of symptoms. The sudden, large blood pressure rises experienced by high spinal cord injury patients during episodes of autonomic dysreflexia place them at high risk for major hypertensive complications such as intracerebral haemorrhage.[11] By attenuating these massive blood pressure rises, prophylactic therapy with prazosin would be expected to reduce the frequency of these catastrophic hypertensive events.

At the dosage regime used in this study, improvement was noted in the individual symptoms that accompany autonomic dysreflexia, but only headache was found to be significantly improved. The lack of statistical significance of the improvements in symptom severity noted in the prazosin group (excepting headache) arise mainly because of the high percentage of patients without symptoms in each particular symptom group, skewing the nonparametric analysis. However when relatively severe symptoms were analysed, prazosin was found to result in reductions in severity in all symptom groups. Moreover, the dose of prazosin used did not produce a significant lowering of resting supine blood presure or adverse side effects. This suggests that higher or more frequent doses may be possible and may achieve a greater benefit.

In summary, improvements have been demonstrated in a number of important parameters of disease severity in patients experiencing the syndrome of autonomic dysreflexia when given prazosin therapy in comparison with placebo. Prazosin was both safe and effective at the dose studied.

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