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. 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. In addition, chronic spinal cord injury patients have enhanced blood pressure rises in response to exogenous infusion of catecholamines and angiotensin II which has been interpreted as reflecting both altered baroreceptor sensitivity and increased vascular reactivity to both alpha-1 and alpha-2 adrenoceptor agonists and to angiotensin II. Baroreceptor reflexes (which tend to suppress rises in blood pressure during infusions of pressor substances) were less variable in tetraplegic patients than controls.

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 ± 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 (±standard deviation) of baseline systolic and diastolic blood pressure levels together with systolic and diastolic blood pressure rise during