Paroxysmal Neurogenic Hypertension and its Prevention in Patients with Cervical Spinal Cord Lesions

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SUMMARY

Ten patients with clinically complete cervical spinal cord transection of traumatic origin were studied. These subjects do not have supraspinal control of their sympathetic outflow and are prone to marked elevations of blood pressure during visceral and somatic stimulation. This is a result of reflex sympathetic activity via the isolated spinal cord. The arterial blood pressures and heart rates of these patients were recorded on separate occasions during elevation of the urinary bladder pressure and before and after treatment with propranolol, labetalol, phenoxybenzamine and guanethidine.

Guanethidine seems to afford the best protection against the marked hypertension occurring during autonomic hyperreflexia. In contrast to the ganglionic blocking agents, it has no anticholinergic or CNS side-effects, and reflex sweating, a valuable indicator of an impending abdominal catastrophe, still occurs.

The finding that negative inotropic drugs, i.e. propranolol, guanethidine and labetalol, reduce the marked elevations in pulse pressure which occur during acute bladder distension in quadriplegics, patients, suggest that inotropic cardiac responses are mediated by cardiac sympathetic nerves which leave the spinal cord above the T5 level.

Autonomic hyperreflexia is a syndrome consisting of an uncontrolled sympathetic response to visceral and somatic stimuli below the level of a high spinal cord lesion. It has an 85% prevalence in quadriplegics and is usually manifested by sudden arterial hypertension, bradycardia, sweating on the face and neck, pilomotor erection and a severe throbbing headache. During the episode, convulsions or haemorrhages (retinal or intracranial) may occur. Hypertension for short periods has been shown to damage blood vessels in experimental animals and the second most common cause of death in patients with chronic spinal cord lesions is cerebrovascular accidents. Resting levels of plasma noradrenaline and adrenaline are significantly lower in quadriplegics than in normal subjects. When hypertension is induced in these patients by bladder stimulation, a significant rise in plasma noradrenaline level results. The urinary excretion of catecholamine metabolites in quadriplegic subjects is significantly greater than in normal people, probably owing to many subclinical, undetected hypertensive episodes. An example of the latter could be the haemodynamic changes accompanying the frequent muscle spasms in the spastic patient. The present study was undertaken to determine the most suitable drug for the prevention of autonomic hyperreflexia, especially since conflicting reports have appeared in the literature.

PATIENTS AND METHODS

In this series of experiments 10 quadriplegic patients were subjected to acute urinary bladder distension with normal saline solution. Their ages varied from 19 to 49 years and all had physiologically complete cervical spinal cord transections between the C4 and C7 levels. Nine were inpatients at the Spinal Unit, H.F. Verwoerd Hospital, Pretoria, while 1 resided at a home in Linden, Johannesburg. In addition to routine physical examination, the following additional examinations were performed: estimations of serum electrolytes, urea, urate, and creatinine levels, liver function tests, a haemogram and an ECG. None of the subjects was found to be suffering from any systemic disease or had received diuretic, hypotensive or adrenergic drugs. (Verbal informed consent was obtained from each subject and this was witnessed by a nursing sister.)

All quadriplegics had an indwelling urinary catheter and bladder filling was the method used to elicit paroxysmal hypertension, since rectal distension and peripheral stimuli are known to be unreliable for this purpose. The catheter was connected to a suspended bottle of sterile normal saline from which the saline was allowed to flow freely into the bladder. The blood pressure was recorded with a Roche Arteriosonde automatic sphygmomanometer and electrocardiographic tracings were made. A sharp reduction in the rate of flow of the saline served to indicate reflex spasm of the bladder. Before the initiation of the experiment the patient was told to report the development of a headache, nasal stuffiness, pilomotor response, sweating or flushing. After hyperreflexia had been elicited, the bladder was emptied fairly rapidly. This procedure was repeated on separate occasions after pretreatment of the patients with blocking dosages of various sympatholytics. As propranolol 0.2 mg/kg is considered a blocking dosage, 10 mg of this drug was administered intravenously. The intravenous administration of labetalol 1.5 mg/kg inhibits the pressor effects of parenterally administered noradrenaline. It was decided to administer a single intravenous dose of 100 mg of this drug to each subject. The usual blocking dose of phenoxybenzamine in man is 1.0 mg/kg. To ensure optimal blockade, 100 mg of phenoxybenzamine was added to 200 ml of 0.9% NaCl and infused intravenously over a period of 1 hour. Bladder distension was started 20
minutes after the administration of propranolol and labetalol and 30 minutes after completion of the infusion of phenoxybenzamine. Oral administration was deemed advisable in the case of guanethidine as its intravenous administration is followed by hypertension which may persist for several hours and is much accentuated by spinal cord section. Even though the absorption of guanethidine varies from 3% to 30% in different individuals a relatively small daily dosage of 20 mg was given to all patients. It was prescribed for at least 14 days, as the effects of the drug are cumulative.

**RESULTS**

Figs 1-4 demonstrate the percentage change in the mean blood pressure with bladder distension between the pretreatment values and those found after the administration of propranolol, labetalol, phenoxybenzamine and guanethidine. Mean blood pressure (MBP) was calculated from systolic and diastolic blood pressure using the formula:

\[
\text{MBP} = \frac{1}{3} \text{pulse pressure} + \text{diastolic blood pressure}
\]

With propranolol the MBP rose higher than the pretreatment value in all the patients. After the administration of labetalol the MBP was significantly higher in 2 patients and very much lower in 1. After phenoxybenzamine the MBP rose in 2 patients, was lower in 1 and essentially unchanged in another. With the exception of 1 patient in whom the MBP remained unchanged, guanethidine lowered blood pressure in all.

The mean changes in pulse pressure and heart rate in the group of subjects studied are shown in Table I.

**TABLE I. CHANGES IN PULSE PRESSURE AND HEART RATE**

<table>
<thead>
<tr>
<th></th>
<th>Pulse pressure (mmHg)</th>
<th>Heart rate (/min)</th>
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<tbody>
<tr>
<td>(a) Pretreatment values before bladder distension</td>
<td>30,7</td>
<td>78,1</td>
</tr>
<tr>
<td>(b) Pretreatment values during bladder distension</td>
<td>68,6</td>
<td>54</td>
</tr>
<tr>
<td>Percentage change from (a)</td>
<td>123,5%</td>
<td>-30,9%</td>
</tr>
<tr>
<td>(c) Values during bladder distension after propranolol</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>Percentage change from (a)</td>
<td>82,4%</td>
<td>-38,5%</td>
</tr>
<tr>
<td>(d) Values during bladder distension after guanethidine</td>
<td>54,3</td>
<td>54,8</td>
</tr>
<tr>
<td>Percentage change from (a)</td>
<td>76,9%</td>
<td>-29,8%</td>
</tr>
<tr>
<td>(e) Values during bladder distension after labetalol</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>Percentage change from (a)</td>
<td>79,2%</td>
<td>-4 %</td>
</tr>
<tr>
<td>(f) Values during bladder distension after phenoxybenzamine</td>
<td>63,3</td>
<td>71</td>
</tr>
<tr>
<td>Percentage change from (a)</td>
<td>106,2%</td>
<td>-9,1%</td>
</tr>
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**DISCUSSION**

Autonomic hyperreflexia in the quadriplegic most commonly results from distension of the pelvic viscera, such as the bladder and rectum, and less frequently follows spontaneous and induced muscle spasm and tactile or thermal stimulation of the skin below the level of the spinal cord lesion. It also occurs with urinary tract
Infections and stones, uterine contractions, ejaculation, urological procedures and angiography. The pathophysiology of the syndrome was described by Kurnick1 in 1956. Contraction of the urinary bladder is the most frequent cause of significant autonomic hyperreflexia. The afferent sensory stimuli arising in this viscus are said to ascend in the spinothalamic tracts and posterior columns of the spinal cord. Reflex motor outflow via neurons in the lateral horns causes spasm of the pelvic viscera, arteriolar spasm (thereby hypertension), pilo-erection and sweating.

In the normal individual these reflexes are partially inhibited by outflow from higher centres. Aortic arch and carotid sinus baroreceptors are stimulated, eliciting a general vascular depressor response. The sinus reflex stimulates the hypothalamic 'sympatho-inhibitory' and 'defence' areas,13 which respectively inhibit adrenergic constrictor activity and activate cholinergic receptors. Adrenergic tone is almost completely inhibited before the sympathetic cholinergic vasodilator system mediates an additional 15-30% of the total decrease in muscle vascular resistance evoked by the sinus reflex. The vagal bradycardia is elicited by the pre-optic region,11 which has been designated as part of the sympatho-inhibitory system.16 In patients with physiologically complete cervical cord transections the failure of these inhibitory reflexes to reach the lateral horn neurons results in vasoconstriction and hypertension. For paroxysmal hypertension to occur the lesion must be above the major splanchnic outflow. Usually the lowest lesion has been at T5 although levels of T6 and T7 have been reported.16 The sudden rise in systemic blood pressure from the reflex arteriolar spasm below the level of the lesion is sensed by the baroreceptors. Afferents from these stretch receptors course in the 9th and 10th cranial nerves and the efferents to the sino-atrial node course in the vagus. Bradycardia results as these pathways are intact in quadriplegic subjects.

Hypertension induced by bladder stimulation is accompanied by a significant rise in the plasma noradrenaline level and by an increase in the urinary excretion of catecholamines and their metabolites.5-10 Studies on plasma dopamine-β-hydroxylase, the enzyme which is released together with noradrenaline from sympathetic nerve terminals but not from the adrenal medulla,16 lend support to the view that paroxysmal hypertensive episodes are the result of increased peripheral sympathetic nervous activity. When sympathetic nervous activity is evoked by bladder stimulation plasma dopamine-β-hydroxylase levels rise,15 but are highest a few minutes after cessation of stimulation and peak blood pressure, probably because after release from adrenergic nerve terminals it is transported in lymph before it enters the systemic circulation.13 After the infusion of noradrenaline in quadriplegics it was found that in order to produce comparable rises in blood pressure the plasma noradrenaline levels required were approximately 8-37 times the levels observed during bladder stimulation.2 Neuronally released noradrenaline thus appears to be responsible for the hypertension due to bladder stimulation. The effectiveness of guanethidine in the present study lends further support to this view. If catecholamines secreted by the adrenal medulla are responsible for the cardiovascular changes during visceral stimulation,2 guanethidine would probably have caused an excessive rise in the blood pressure. Firstly, it has little effect on the catecholamine content of the adrenal medulla.12 Secondly, chronic administration of guanethidine produces a supersensitivity of effector cells that reaches a maximum in 10-14 days20 and for this reason
it is contraindicated in the presence of a phaeochromocytoma.\(^a\)

Permanent protection from the dangers of autonomic hyperreflexia can be achieved through cordectomy, pelvic or pudendal nerve section, posterior rhizotomy, or intrathecal injection of alcohol.\(^b\) Various drugs have been applied in the prevention of paroxysmal hypertension in quadriplegic patients. Kurnick\(^1\) found the hypertension to be sensitive to ganglionic blocking agents but resistant to \(\alpha\)-adrenergic blocking drugs. The ganglion blockers, such as hexamethonium, megamylamine, pentolinium and trimetaphane, are effective, but their anticholinergic side-effects make them unsuitable as prophylactic agents. Also, they control the bradycardia, pilomotor erection and bladder spasticity more readily than the hypertension.\(^2\) Alpha-adrenergic blocking drugs are more effective in blocking the effects of circulating catecholamines than those produced by neurally released noradrenaline.\(^3\) The wide acceptance of phenoxybenzamine in the treatment of autonomic hyperreflexia is based on its reported efficacy in 2 cases.\(^4\) Phentolamine is primarily a direct vasodilator\(^5\) and is not more than 20% as active after oral administration as it is when given parenterally.\(^6\)

The drugs used in the present study were chosen on the following grounds: phenoxybenzamine because of the controversy on its efficacy;\(^7\) labetalol, a drug that blocks both \(\alpha\) - and \(\beta\)-adrenoceptors and lacks a direct vasodilator component, because of the suggestion that it is the only \(\alpha\)-blocker that inhibits responses to neurally released noradrenaline more effectively than those to systemically administered noradrenaline;\(^8\) propranolol because it is often prescribed to quadriplegic patients, and also to compare its effects with those of labetalol; and guanethidine, an \(\alpha\)-adrenergic blocking-agent which prevents the release of effective quantities of noradrenaline in response to sympathetic activity, because in sharp contrast to ganglionic blocking agents it does not interfere with tonic parasympathetic activity.\(^9\) Because of this, parasympathetically mediated contraction of the bladder wall and inhibition of the internal sphincter is facilitated and reflex sweating is not inhibited. Since autonomic hyperreflexia is an alarm signal of excessive activity of a viscus in the anesthetic area of the body,\(^10\) the sweating is a valuable indicator of an impending abdominal catastrophe. With guanethidine, postural hypotension is not so disabling as that associated with ganglionic blockade\(^11\) and with quadriplegic patients exertional hypotension is of little importance. Likewise, failure of ejaculation is of lesser importance than in the normal subject. Guanethidine, in contrast to reserpine, does not cause mental changes, since it penetrates the central nervous system very poorly.\(^12\)

In the present study propranolol caused an exaggerated rise in the blood pressure, probably because it prevents catecholamine-induced \(\beta\)-mediated vasodilatation, while at the same time allowing \(\alpha\)-mediated vasoconstriction. Labetalol, being 4-8 times more potent at \(\beta\) - than at \(\alpha\)-receptors,\(^13\) had similar effects to propranolol in 2 patients. In 1 patient, who received labetalol 2.8 mg/kg, the rise in blood pressure was significantly reduced, probably because \(\alpha\)-blockade manifested fully. The relative increase in the blood pressure in 2 patients treated with phenoxybenzamine can possibly be ascribed to its inhibition of the inactivation of noradrenaline.\(^14\) Guanethidine failed to reduce the rise in blood pressure in only 1 patient, possibly because of inadequate absorption of the drug\(^15\) in this individual.

Elevation in peripheral resistance, i.e. vasoconstriction, is characterized by primary increase in systolic and diastolic pressures, with little increase or even a reduction in pulse pressure. On the other hand, marked elevation in systemic arterial pulse pressure is characteristic of increased systolic ejection from the heart due to the inotropic effects of cardiac sympathetic innervation.\(^16\) The marked elevations in pulse pressure in patients with lesions above the T5 level cannot be explained solely by increased vasoconstriction and decreased heart rate, but involve also inotropic cardiac responses, mediated by cardiac sympathetic nerves which leave the spinal cord at the T1-T5 levels.\(^17\) In the present study the average increase in pulse pressure during bladder distension before medication was 123.5% while the average decrease in heart rate was 30.9%. The negative inotropic and chronotropic drugs, i.e. propranolol, guanethidine and labetalol, all reduced this rise in pulse pressure by a third or more. The relative decrease in heart rate, however, was much smaller. Propranolol reduced the heart rate by an additional 7.6%, guanethidine left it relatively unchanged and labetalol almost prevented bradycardia during bladder distension. Phenoxybenzamine, which does not inhibit the chronotropic and inotropic effects of the catecholamines on the mammalian myocardium,\(^18\) had a much smaller reducing influence on the pulse pressure. These results suggest that the marked elevations in pulse pressure occurring during episodes of autonomic hyperreflexia are to a great extent brought about by inotropic cardiac responses, mediated by the preganglionic fibres to the heart leaving the spinal cord at the T1-T5 levels.

I should like to thank the patients who acted as subjects in these investigations. I am indebted to Sister E. Heunis and the nursing staff of the Spinal Unit, H.F. Verwoerd Hospital, for their continued interest and help, Dr E. van Wyngaard, Superintendent of the H. F. Verwoerd Hospital for permission to work in the Unit, Professor L. S. De Villiers of the Department of Chemical Pathology for the special investigations, and Mmes A. N. Malherbe and S. E. du Preez for assisting in the preparation of this manuscript. Without the valuable technical assistance of Mr J. C. Avenant this project would not have been possible.

REFERENCES

Mumps Virus and Ovarian Cancer

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SUMMARY

Thirty-four patients with carcinoma of the ovary were compared with controls matched for age, sex and racial origin. Previous mumps infection was determined by taking a history from the patient, by complement fixation test and by estimating neutralizing antibody titre. No significant differences between the two groups were found for any of the three methods used to estimate previous exposure to mumps virus. Therefore this study did not confirm previous hypotheses that mumps infection confers a significant degree of protection against the development of ovarian cancer. A relatively small proportion of cases could possibly be due to lack of such protection, but in this study not more than 30% at the 5% fiducial limit.

Malignant ovarian tumours are the fourth most important cause of deaths due to cancer in the human female. They are the third commonest malignant tumour of the female genital tract, comprising between 12.3% and 19.5% of that group of tumours. According to Barber and Kwon they are the commonest cause of death from malignant gynaecological tumours. Some 80-95% of all ovarian tumours are epithelial in origin, arising from the coelomic epithelium.

The average age at diagnosis varies between 48.5 and 58.9 years in different reports. The incidence of the disease is low until the age of 40 years, rising to a peak in the 6th and 7th decades of life.

Despite improvement in surgical and irradiation techniques and in chemotherapy, the prognosis remains poor. The survival rate in patients with ovarian malignant tumours is lower than that of other malignant tumours of the female genital tract. The 5-year survival rate is reported as 13 - 32.5% in various studies.

The aetiology is unknown and considerable effort is being devoted to defining common factors in these patients. Very marked differences in the incidence of ovarian cancer have been found in different geographical locations. The tumour is relatively uncommon in Japan and Chile, but very common in Scandinavia, the USA and Israel. No reason for the differences has been suggested. The incidence is higher among women of upper socio-economic classes, and a correlation exists between ovarian can-