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THE PRESSOR ACTIONS OF NORADRENALINE AND ANGIOTENSION II IN CHRONIC AUTONOMIC FAILURE TREATED WITH INDOMETHACIN

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1 Indomethacin treatment of postural hypotension in four patients with chronic autonomic failure increased their pressor supersensitivity to intravenous noradrenaline without causing fluid retention.

2 All patients were supersensitive to angiotensin II in spite of normal levels of plasma renin activity in the supine position and therefore (by inference) of angiotensin II. This suggests that in autonomic failure, the degree of angiotensin receptor occupancy by endogenous angiotensin II is not important in determining pressor sensitivity to exogenous angiotensin II. Indomethacin increased the pressor supersensitivity to angiotensin II in all patients

3 Indomethacin treatment decreased supine plasma renin activity to 50% of the level present before indomethacin treatment.

4 Indomethacin increased the lying but not the standing blood pressure. The failure to raise the standing pressure may be the result of the additional postural stress overcoming any vasoconstriction resulting from the increased sensitivity of vascular receptors to noradrenaline. The decrease in plasma renin activity could also contribute to the failure of indomethacin to prevent a fall in blood pressure on standing.

5 In our patients the excretion of the main urinary metabolite (PGFM) of prostaglandin $F_{2\alpha}$ was higher than recorded previously in normal controls. During treatment with indomethacin, plasma indomethacin levels were in the range at which inhibition of prostaglandin synthesis occurs and the excretion of PGFM was decreased.

6 Indomethacin was not effective in the treatment of postural hypotension in these patients with autonomic failure.

Introduction

In chronic autonomic failure, postural hypotension may be a disabling feature. It results from degeneration of the sympathetic nervous system with defective vasoconstriction on standing (Bannister, Ardill & Fentem, 1967). The autonomic failure may occur alone (Bradbury & Eggleston, 1925) (idiopathic postural hypotension) or together with parkinsonism (Graham & Oppenheimer, 1969) or other neurological abnormalities (multiple system atrophy or Shy Drager Syndrome) (Shy & Drager, 1960; Bannister & Oppenheimer, 1972).

In all these conditions, the postural hypotension can be treated by blood volume expansion by body tilting, reduction of venous pooling in the legs by mechanical aids, the use of pressor drugs to produce vasoconstriction and mineralocorticoids (Bannister, Ardill & Fentem, 1969). None of these measures is completely successful (Davies, Bannister & Sever, 1978). Therefore a report (Kochar & Itskovitz, 1978) that postural hypotension was improved by indomethacin prompted further study, especially since the diagnosis of autonomic failure in that report was not confirmed by physiological testing (Bannister, Davies & Sever, 1978). Indomethacin inhibits the synthesis of prostaglandins (Vane, 1971). Also in normal subjects, indomethacin may sensitize vascular receptors to pressor amines (Guthrie, Messerli, Kuchel & Genest, 1976) to which patients with autonomic failure are supersensitive (Wilcox & Aminoff, 1976; Bannister, Davies, Holly, Rosenthal & Sever, 1979). Fludrocortisone, a mineralocorticoid, has been shown to increase the pressor sensitivity of patients with autonomic failure to intravenous noradrenaline and to improve their postural hypotension (Davies, Bannister, Sever & Wilcox, 1979). Indomethacin may have similar effects. In order to obtain more information about the actions of indomethacin, we have studied the changes in blood pressure, the pressor responses to intravenous noradrenaline and angiotensin II and changes in

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urinary prostaglandin excretion after indomethacin treatment in four patients with postural hypotension caused by chronic autonomic failure.

Methods

Two male (cases 1 and 4) and two female (cases 2 and 3) patients aged 60, 52, 69 and 39 years were treated. All had postural hypotension, which was shown to be due to chronic autonomic failure. Three patients also had parkinsonism (cases 2, 3 and 4). Bladder dysfunction and pyramidal tract signs were present in cases 1 and 2.

The neurological diagnosis in each case was chronic autonomic failure with multiple system atrophy of varying degree (Shy Drager syndrome). Testing of autonomic function in all patients showed marked postural hypotension, loss of systolic overshoot in the Valsalva response and loss of a pressor response to stress, indicating a sympathetic efferent lesion (Bannister *et al.*, 1967). All patients were supersensitive to intravenous noradrenaline and all had low recumbent plasma noradrenaline levels which failed to rise on tilt (Bannister *et al.*, 1979; Davies *et al.*, 1979). All patients were admitted to hospital for the study which had their informed consent.

Throughout the study, patients ate a diet containing 90 mmol Na^+ per day. Body weight, fluid intake and output, urinary sodium and potassium were measured daily. Blood pressure (lying and after 5 min standing) was recorded with a sphygmomanometer daily at 06.00 h and 18.00 h because these were the times at which symptoms from postural hypotension were, respectively, the greatest or the least. Haematocrit, plasma sodium and potassium and plasma proteins were measured every third day.

Indomethacin treatment and drug infusions

For the first 7 days of the study, no drugs were given. On day 7 at 18.00 h a loading dose (50 mg by mouth) of indomethacin was given followed by 25 mg at 08.00, 14.00 and 18.00 h from days 8 to 11. This was increased to 50 mg at 08.00, 14.00 and 18.00 h from days 12 to 14. On day 7, before indomethacin therapy was begun and again on day 14 at the same time of day as previously, log dose response curves for increases in systolic blood pressure after, respectively, intravenous noradrenaline (noradrenaline bitartrate, Winthrop Laboratories) and angiotensin II (Hypertensin, Ciba-Geigy Ltd) were obtained. The blood pressures after infusion of these drugs were compared with those after 5% glucose placebo infusions. The patients were recumbent during the drug infusions which were given through intravenous cannulae (Abbocath 18G, Abbot Laboratories) in an antecubital vein using a constant infusion pump (Meltech Ltd, London). Blood pressures were recorded at 5 min intervals during an initial resting period of 45 min and then at 1 min intervals during the drug infusions using a Bosomat II automatic blood pressure recorder (Bosch and Sohn, Fabrik Medizinischer Apparate D 7455, Jungingen). The instrument was calibrated at frequent intervals against a sphygmomanometer (Davies *et al.*, 1978). Samples for plasma renin activity were taken (blood (5 ml), cold tubes, EDTA anticoagulant) after 35 and 45 min recumbency prior to the drug infusions. Plasma renin activity was measured by radioimmunoassay (Boyd, Adamson, Fitz & Peart, 1969).

Measurement of plasma indomethacin

On days 13 and 14 (for cases 2, 3 and 4), 1.5 h after the 14.00 h dose of indomethacin (50 mg), blood (5 ml) was taken into ice-cold tubes containing lithium heparin as anticoagulant for measurement of plasma indomethacin levels. Plasma was separated by centrifugation at 4°C, (2000 *g*, 10 min, M.S.E. Coolspin). Plasma (1 ml) was equilibrated with citrate buffer (trisodium citrate 0.1 M, 29.5 ml, citric acid 0.1 M, 20.5 ml, water, 50 ml, pH 4.8) (1 ml), water (1 ml) and internal standard (1 ml) containing mefenamic acid in water (5 $\mu g\ ml^{-1}$). Diethyl ether (5 ml) was added and the mixture was vortexed for 15 min. The phases were separated by standing or centrifugation and the ethereal phase removed and taken to dryness under nitrogen. The organic residues were redissolved in HPLC mobile phase (acetonitrile:1 M acetic acid, 3:4, v/v) (100 μl) and aliquots (30 μl) were analysed (flow rate 2.4 ml min^{-1}, water's 600 Delivery Pump, Water's U6K Injector, Water's O.D.S. Column, 25 × 3.9 cm, Cecil UV Detector wavelength 270 nm).

Measurement of urinary prostaglandin excretion

Urine was collected in polypropylene bottles and kept at 4°C, on days 6 and 7, 13 and 14 (cases 2, 3 and 4). Prostaglandin excretion was assessed by the measurement of 5α,7αdihydroxy-ll-ketotetranorprostan-l, 16-dioic acid (PGFM, the main urinary metabolite of $PGF_{2\alpha}$) by stable isotope dilution and combined gas chromatography–mass spectrometry (Brash, Baillie, Clare & Draffan, 1976).

Statistical analysis of data

The blood pressure values and urinary PGFM excretion before and after indomethacin treatment were compared using paired *t*-tests. Log dose response curves for increases in blood pressure produced by noradrenaline and angiotensin II were

constructed by the method of least squares and tested for non-parallelism.

Results

Body weights, plasma proteins, sodium and potassium did not change during the study (see Table 1). However, after indomethacin, urinary sodium was decreased from 99 ± 23 to 87 ± 32 mmol 24 h^{-1} (mean $\pm$ s.d., $P < 0.0125$). Plasma renin decreased from 2800 ± 1748 to 876 ± 1412 (pmol angiotensin I generated l^{-1} h^{-1}, mean $\pm$ s.d., $P < 0.05$) after indomethacin. The mean plasma indomethacin levels for three patients (cases 2, 3 and 4) were 1.8 and 1.6 μmols l^{-1} on the last 2 days of the study (days 13 and 14, Table 1). For the same three patients, the excretion of PGFM on the last 2 days of the pre-treatment period (days 6 and 7) averaged 71.8 ± 9.7 and 76.4 ± 2.7 nmol 24 h^{-1}, respectively (mean $\pm$ s.d., 1 nmol PGFM = 328 ng, Table 1). After indomethacin, excretion of PGFM was 37.6 ± 5 ($P < 0.05$) and 37.8 ± 5.5 ($P < 0.025$) nmol 24 h^{-1} on days 13 and 14 respectively, a 50% decrease.

Log dose-response curves for the changes in systolic blood pressure caused by noradrenaline or angiotensin II infusions in the four patients before and after indomethacin treatment are shown in Figures 1 and 2, respectively. The effect of indomethacin on the response to noradrenaline was to produce a parallel shift to the left of the curves in all the patients. In all patients, after indomethacin the dose response curve for angiotensin II was situated to the left of that obtained at the end of the pretreatment period: the shift was marked in case 2 (Figure 2).

The average mean blood pressures recorded at 06.00 and 18.00 h for the 7 days before and after indomethacin treatment are shown in Figure 3. At all times, the pressures with the patients lying were higher than the pressures after standing (in each case, $P < 0.0005$). During indomethacin treatment, the pressure at 18.00 h with the patients lying was higher than before indomethacin (13.8 ± 2.2 kPa and 18.8 ± 3.2 kPa, respectively, $P < 0.05$, 1.35 kPa = 10 mm Hg.). There was no significant difference in the standing pressures after indomethacin compared with the pretreatment period.

Discussion

Indomethacin increased the sensitivity of our patients to noradrenaline, as shown by the shift to the left of the log dose-response curves after treatment with indomethacin. All these patients were supersensitive to noradrenaline before indomethacin and for each patient the degree of supersensitivity was identical to that in a previous study (Davies, Bannister, Sever & Wilcox, 1979). Therefore, although no formal control for the administration of indomethacin was made, it is likely that the change in sensitivity was due to indomethacin. Indomethacin increases the pressor responsiveness to noradrenaline in normal subjects (Guthrie *et al.*, 1976) and in patients with Bartter's Syndrome (Silverberg, Mennes & Cryer, 1978).

The increased sensitivity to noradrenaline may have been due to inhibition of prostaglandin synthesis by indomethacin. Various prostaglandins

Table 1 Plasma indomethacin, urinary PGFM and other parameters before and after indomethacin

Measurement	*Before*		*After*
Body weight (kg)	61.7 ± 11		61.5 ± 11
Haematocrit	0.40 ± 0.06		0.40 ± 0.05
Plasma proteins (g l^{-1})	77.3 ± 5		76 ± 5
Plasma sodium (mmol l^{-1})	138.8 ± 3		139 ± 2
potassium (mmol l^{-1})	4.2 ± 0.2		4.19 ± 0.3
Urinary sodium (mmol 24 h^{-1})	99 ± 23		87 ± 32***
potassium (mmol 24 h^{-1})	2.1 ± 1.0		1.9 ± 0.8
Plasma renin (pmol l^{-1} h^{-1})	$2,800 \pm 1,748$		876 ± 1412*
Plasma indomethacin (μmol l^{-1})	—	(Day 13)	1.8 ± 1.2
	—	(Day 14)	1.55 ± 0.9
Urinary PGFM (nmols 24 h^{-1})	71.8 ± 9.7 (Day 6)	(Day 13)	37.6 ± 5*
	76.4 ± 2.7 (Day 7)	(Day 14)	37.8 ± 5.5**

Values represent the means $\pm$ s.d. for interindividual differences for the 7 days before and during indomethacin treatment except for plasma indomethacin and urinary PGFM which were measured on the days shown in parentheses. Plasma renin activity expressed as pmols of angiotensin I generated l^{-1} h^{-1}. (patients recumbent—see **Methods**).

*$P < 0.05$, **$P < 0.025$, ***$P < 0.0125$, paired t-tests.

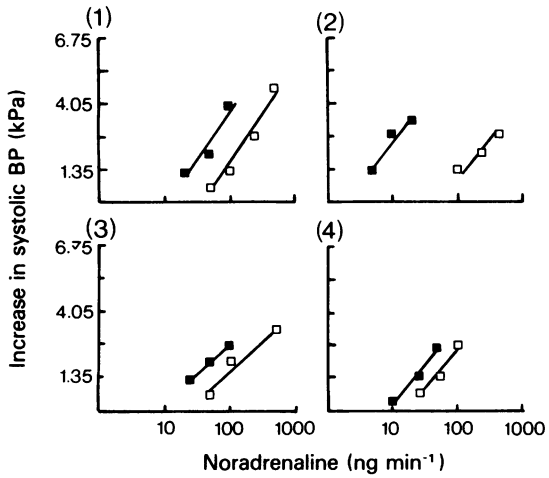

Figure 1 Parallel shift to the left of the log dose-response curves for noradrenaline after treatment with indomethacin. Doses of noradrenaline shown as linear values but on a log scale (abscissa). Numbers in parentheses indicate individual cases. □ before, ■ after indomethacin. 1.35 kPa = 10 mmHg.

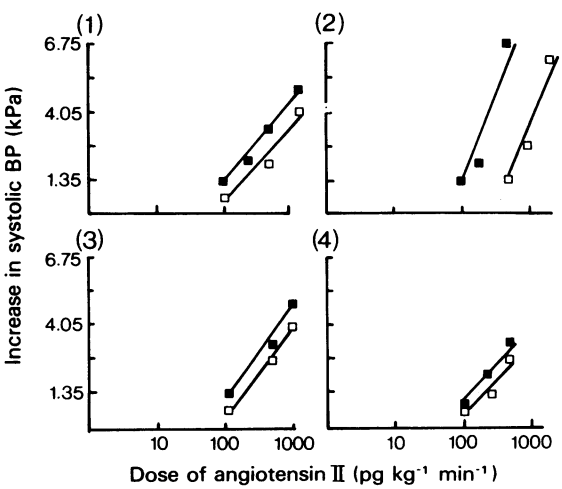

Figure 2 Dose-response curves for angiotensin before and after treatment with indomethacin. Doses of angiotensin shown as linear values but on log scale (abscissa). Numbers in parentheses indicate individual cases. □ before, ■ after indomethacin. 1.35 kPa = 10 mmHg

can interact with the sympathetic nervous system in several ways (Horton, 1973), either presynaptically (Hedqvist, 1970) to decrease the amount of noradrenaline released by nerve stimulation, or by antagonizing the action of sympathomimetic amines at postsynaptic receptors (Clegg, 1966). Removal of these inhibitory actions of prostaglandins could have

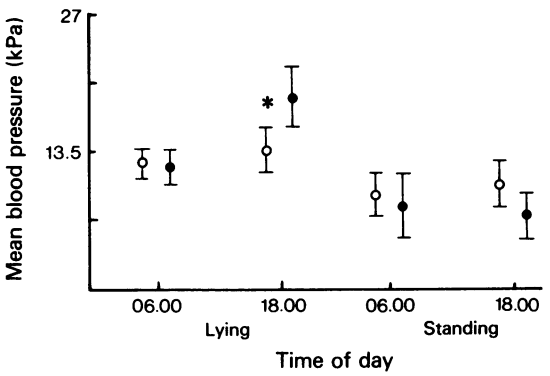

Figure 3 Average mean blood pressures with patients lying or standing before and after indomethacin treatment. Values represent the means ± s.d. for interindividual differences in the average mean blood pressure for the 7 days before indomethacin and the 7 days treatment period. ○ before, ● after indomethacin. 1.35 kPa = 10 mmHg. *BP higher after indomethacin $P < 0.05$.

been a factor in the increase in lying blood pressure after indomethacin treatment. The plasma levels of indomethacin were probably sufficient for inhibition of prostaglandin synthesis which may need only a concentration of 0.28 μM depending upon the system and prostaglandin involved (Rane, Delz & Seyberth, 1977; Flower, 1974). The urinary excretion of PGFM gave an approximate index of prostaglandin synthesis. In our patients PGFM excretion was higher than in normal subjects (Brash *et al.*, 1976; Brash, Baillie, Clare & Draffan, 1978). Indomethacin decreased PGFM excretion by about 50% which is less than described in normal subjects (Brash *et al.*, 1978). Higher than normal urinary excretion of prostaglandin E, which was decreased by indomethacin has been shown in a single case of idiopathic postural hypotension (Zwada & Kirschenbaum, 1979). In that case, indomethacin also decreased urinary sodium excretion. In our patients urinary sodium was slightly decreased but there was no apparent fluid retention becasue body weight, haematocrit, plasma proteins and sodium did not change after indomethacin.

The effect of indomethacin on pressor supersensitivity to angiotensin II was not as clear as for noradrenaline. Although in all cases the log dose response curves after indomethacin lay to the left of that before indomethacin, only for 1 patient (case 2, Figure 2) was this shift marked. Indomethacin increases the pressor responsiveness to angiotensin II in normal man (Guthrie *et al.*, 1976; Speckart, Zia, Zipser & Horton, 1977). However. our patients were supersensitive to angiotensin II before indomethacin treatment so that in cases 1, 3 and 4, large increments

in sensitivity were impossible. Case 2 was less sensitive to angiotensin II than the other patients before indomethacin and so a greater increase in sensitivity was possible. In this patient indomethacin treatment also appeared to lower the threshold response to angiotensin II.

The usual explanation for increased pressor responsiveness to angiotensin is that low endogenous levels lead to decreased receptor occupancy and so greater availability of receptors for administered angiotensin II. Levels of endogenous angiotensin II depend upon plasma renin activity (Peach, 1977). In our patients, before indomethacin, plasma renin levels were normal, but supersensitivity to angiotensin II was marked. This may mean that in autonomic failure the degree of receptor occupancy by endogenous angiotensin II is not important—the number of receptors may have increased or their nature may have changed. This situation has not to our knowledge been described previously. However, changes in blood pressure in response to intravenous pressor agents may not give a true reflection of the status of vascular receptors for these pressor substances. It is known, however, that even in the presence of autonomic degeneration plasma renin activity in the lying position is often normal (Bannister, Sever & Gross, 1977). As expected, indomethacin decreased plasma renin levels, (Speckart *et al.*, 1977). A decrease in plasma renin activity could also contribute to the failure of indomethacin to prevent a fall in blood pressure on standing.

Indomethacin did not reduce the postural hypotension in any of the patients. The blood pressure was recorded at 06.00 and 18.00 h because these were the times at which the symptoms from the postural hypotension were greatest or least, respectively. The lying blood pressure at 18.00 h was increased. Possibly, the greater vascular receptor sensitivity to remaining stores of noradrenaline was only effective in vasoconstriction with the patients supine, but was insufficient to overcome the stress of standing. This postural stress could have been increased by the ganglion blocking action of indomethacin (Abraham & Takare, 1975) since postural hypotension is a side-effect of ganglion blockade (Volle & Koelle, 1975). Postural hypotension is not usually seen in normal subjects or patients treated with indomethacin, but could occur in autonomic failure which may already be associated with ganglionic degeneration (Bannister & Oppenheimer. 1972). The decrease in plasma renin activity may also have been important in overcoming any potential benefits of indomethacin treatment.

Indomethacin increased the blood pressure in hypertensive (Patak, Mookerjee, Bentzel, Hysert, Babe & Lee, 1975) and normal subjects (Nowak & Wennalm, 1978, Wennalm, 1978). In one study (Nowak & Wennalm, 1978), the blood pressure was returned to normal by infusion of prostaglandin E_1 and this was interpreted as evidence for the pressor effect of indomethacin being due to inhibition of prostaglandin synthesis although a different mechanism was possible (Wennalm, 1978). These studies (Nowak & Wennalm, 1978; Wennalm, 1978) were done with subjects supine, thus obscuring the effects on blood pressure or postural stress, decreased plasma renin activity or ganglion blockade due to indomethacin although the latter may be insignificant in subjects without sympathetic degeneration. Reports (Kochar & Itskovitz, 1978; Zwada & Kirschenbaum, 1979) claiming a reduction of postural hypotension after indomethacin treatment failed to prove the diagnosis of autonomic failure by physiological testing (Bannister *et al.*, 1967) or measurement of plasma noradrenaline levels (Bannister *et al.*, 1979). Two of the four patients in one study (Kochar & Itskovitz, 1978) had standing blood pressures within the normal range for their ages (Johnson, Smith, Spalding & Wolner, 1965) and in the other (Zwada & Kirschenbaum, 1979) no blood pressure results were given. Previously, (Bannister *et al.*, 1978) we did not find any improvement after indomethacin in the postural hypotension in three fully diagnosed cases of the Shy Drager syndrome. However, in one study in which the diagnosis was proven, benefit did occur during the use of fludrocortisone and flurbiprofen in combination (Perkins & Lee, 1978).

In this study, the greater than normal excretion of urinary PGFM before indomethacin treatment suggests that prostaglandins of various series might be involved in the pathogenesis of postural hypotension. However, the failure of indomethacin to affect the standing blood pressure suggests that, in our patients, prostaglandins did not have an important effect in causing the postural hypotension. Indomethacin decreased the urinary excretion of PGFM. Thus, it is likely that it affected similarly other prostaglandins for it inhibits the synthesis of all the prostaglandin series (Flower, 1974), thromboxanes (Ali, Cerskus, Zamecnik & McDonald, 1977) and prostacyclin (Moncada, Higgs & Vane, 1977). Therefore the action of indomethacin in our patients is difficult to interpret for it may affect the synthesis of pressor and vasodepressor (e.g. E prostaglandins or prostacyclin) compounds.

In conclusion, we have shown that indomethacin may increase the sensitivity of vascular receptors to noradrenaline in chronic autonomic failure, but increased only the lying blood pressure. Lack of improvement in the standing blood pressure could be due to a decrease in plasma renin activity, or the ganglion blocking actions of indomethacin in addition to the postural stress. Indomethacin

decreased urinary prostaglandin excretion but its effects in autonomic failure could be due to other actions.

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