Calcium antagonists decrease adrenal and vascular responsiveness to angiotensin II in normal man

J. A. MILLAR, KATHLEEN McLEAN AND J. L. REID
University of Glasgow, Department of Materia Medica, Stobhill General Hospital, Glasgow, Scotland, U.K.

Summary

1. The effect of the calcium antagonist nifedipine on the pressor and aldosterone responses to angiotensin II was studied in six normal subjects.

2. Blood pressure, pulse rate and plasma aldosterone, potassium and cortisol were measured during paired consecutive infusions of angiotensin II (5, 10 and 20 ng min⁻¹ kg⁻¹) on two separate occasions. Nifedipine (20 mg by mouth) was given, 30 min before the second set of infusions.

3. After nifedipine there were reciprocal changes in supine resting blood pressure (−7 mmHg) and pulse rate (+18 min⁻¹) and a significant decrease in the pressor response to angiotensin II (P < 0.05; Wilcoxon signed rank test).

4. Basal levels of aldosterone were not changed by nifedipine, but the response to angiotensin II was significantly attenuated (P < 0.05). Nifedipine had no effect on plasma potassium or cortisol.

5. Transmembrane movement of calcium is involved in the aldosterone response to angiotensin II in man. Calcium antagonists may lower blood pressure via decreased adrenal responsiveness to angiotensin II as well as by peripheral vasodilatation.

Key words: aldosterone, angiotensin II, calcium antagonists, nifedipine.

Introduction

Binding of angiotensin II to its receptor in the adrenal zona glomerulosa stimulates aldosterone biosynthesis and release [1]. The mechanism of this effect is unknown, but there is evidence that adrenal steroidogenesis is calcium dependent [2] and that the aldosterone response to angiotensin II is associated with intracellular accumulation of calcium [3, 4]. Calcium antagonists inhibit entry of calcium into cells and decrease release of peptide and steroid hormones from several endocrine organs, in addition to their well-known inhibition of excitation-contraction coupling [5-7]. We report here the effect of nifedipine on the blood pressure and aldosterone response to angiotensin II in normal subjects.

Materials and methods

Clinical studies

Six normal male subjects aged 19–40 years (mean 32 years) participated after giving informed written consent. Each subject was studied while fasting on two occasions, separated by at least 2 weeks. Basal blood samples were taken via an indwelling venous cannula after 30 min rest with the subjects supine. Freshly prepared angiotensin II amide solution in normal saline (Hypertensin, CIBA) was then infused via a separate venous cannula, at rates of 5, 10 and 20 ng min⁻¹ kg⁻¹, each for 30 min. The infusion was repeated after an interval of 1 h. Nifedipine (Adalat, Bayer U.K. Ltd.; 20 mg by mouth) was given on one occasion only, 30 min before the second infusion. Blood pressure and pulse rate were measured at 10 min intervals (Arteriosonde; Roche Products Ltd) and blood samples for aldosterone, potassium and cortisol were taken before each increment in infusion rate. Samples for nifedipine were also taken during the second infusion.

Laboratory methods

Aldosterone was measured by direct radioimmunoassay [8] with materials supplied in kit.
form by International CIS (St Quentin, France). All samples were assayed in duplicate in one batch.

Plasma cortisol was measured by gas-liquid chromatography (glc) [9]. Nifedipine was also measured by glc using the method of Kondo *et al.* [10] with minor modifications.

Serum potassium was measured by flame photometry.

**Statistical analyses**

Differences in basal values of blood pressure, pulse rate and plasma aldosterone during nifedipine treatment were assessed by the paired *t*-test. Log-infusion rate–response curves to angiotensin II were calculated by linear regression with the method of least squares. Changes in response were assessed by calculating the gradient of the log-linear regression and analysing these results by the Wilcoxon signed rank test. Both within- and between-day differences in the responses were analysed. Mean blood pressure was computed as diastolic blood pressure plus one-third of the pulse pressure.

**Results**

No between- or within-day variation in either pressor or aldosterone responses to angiotensin II was observed.

Nifedipine caused a slight decrease in diastolic and mean blood pressure in five of the six subjects (diastolic blood pressure, −7 mmHg; mean blood pressure, −5 mmHg), and a corresponding increase in pulse rate (18 min⁻¹), but these changes failed to reach statistical significance. There was a significant decrease (*P* < 0.05) in the pressor effect of angiotensin II after administration of nifedipine in all subjects (Fig. 1a). The effect was most obvious at the lower rates of infusion of angiotensin II. The ratios (nifedipine: control) of pressor effects (diastolic) were 0.3, 0.5 and 0.9 at 5, 10 and 20 ng min⁻¹ kg⁻¹ respectively.

Plasma aldosterone returned to basal levels in the interval between infusions of angiotensin II on both control and treatment days (control, 273 to 117; nifedipine 259 to 123 pg/ml). Hence aldosterone clearance from plasma was not altered by treatment with nifedipine, and basal aldosterone levels were similar on both days. There was a significant decrease in the aldosterone response to angiotensin II after nifedipine in all subjects (*P* < 0.05). The effect was most marked at the higher rates of infusion (Fig. 1b).

The ratios of aldosterone responses at each rate of infusion as above were 0.91, 0.25 and 0.41.

Results for potassium and cortisol levels are shown in Fig. 1c, 1d. Potassium levels were generally lower during the second infusion, but nifedipine had no additional effect. Plasma cortisol was raised at the beginning of the experiments and decreased during both infusions of angiotensin II. There was no difference in cortisol levels when nifedipine was given. Blood nifedipine levels were maintained at therapeutic levels for the duration of the infusions.

**Discussion**

This study has demonstrated that the calcium antagonist nifedipine causes a shift to the right of both the pressor and aldosterone dose–response curves to angiotensin II in man. Although the
effect in each case appeared to be dependent on the rate of angiotensin II infusion, the full range of responses would be required in order to state categorically that the shift was non-parallel.

Only limited conclusions may be drawn from the change in the pressor dose–response. Nifedipine is a potent vasodilator and decreases peripheral resistance by 17% in normal subjects [11]. Such an effect was manifested here by a fall in blood pressure and increase in pulse rate in five subjects. We have observed similar and statistically significant changes in blood pressure and pulse rate in nine normal subjects given nifedipine as part of a double-blind placebo-controlled trial (unpublished work). Hence the basal haemodynamic state after nifedipine was altered in a direction likely to produce a decreased response to pressor agents. Although it is possible that nifedipine interferes with the action of angiotensin II on vascular smooth muscle, the observed effects could be partially or wholly due to drug-induced vasodilatation or increased occupancy of vascular smooth muscle receptors by endogenous angiotensin II.

The results pertaining to aldosterone permit more certain interpretation. Basal levels of aldosterone were similar to control when nifedipine was given, and no effect on clearance of aldosterone from plasma was apparent. Contributions from two other potent stimuli to aldosterone secretion, K+ and adrenocorticotropic hormone (ACTH), were assessed by measuring serum K+ and cortisol. After nifedipine mean plasma K+ was 0.1, 0.2 and 0.3 mmol/l less than corresponding control values at each rate of infusion of angiotensin II as given above, but these differences were not statistically significant. During infusion of K+ relatively large increases in circulating aldosterone can occur with only modest increases in K+ [12]. Thus it is not possible to exclude a potassium effect, though we consider it unlikely. ACTH release is inhibited by angiotensin II at similar rates of infusion to those used here [13], and this effect in combination with normal diurnal variation provides an explanation for the observed changes in serum cortisol during the angiotensin infusions. No additional effect was seen with nifedipine. This implies that pituitary ACTH secretion is not calcium dependent, as appears to be the case for thyroid- and follicle-stimulating hormones [6]. It should be noted that the rates of infusion of angiotensin used correspond to the upper range of physiological levels of endogenous circulating angiotensin II and above.

These studies indicate that inward transmembrane flux of the calcium ion is required for expression of the aldosterone response to angiotensin II in man. Such a requirement may be present at many stages in the sequence of events leading to increased release of aldosterone. Since calcium influx is required for the active secretion of some hormones [14], the effect of nifedipine does not necessarily occur at a point before activation of the biosynthetic pathway. These results are in accord with experiments using cultured rat adrenal zona glomerulosa cells [3, 4]. Fakunding and Catt [4] showed that both cellular accumulation of Ca2+ and the aldosterone response to the addition of angiotensin II to the culture medium are inhibited by verapamil (0.1–100 µmol/l) and also by lanthanum, which blocks calcium channels by a separate mechanism [15].

Calcium antagonists decrease blood pressure in both normal and hypertensive subjects and have potential application in the long-term treatment of hypertension [16, 17]. Our data suggest that the hypotensive effect of this class of drugs may be due in part to reduced adrenal responsiveness to circulating angiotensin II, secondary to interruption of a calcium-dependent mechanism for adrenal aldosterone secretion, as well as by peripheral vasodilatation. The last-named tends to decrease blood pressure per se but also leads to reduced vascular sensitivity to angiotensin II.

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References


