Hormonal and blood pressure changes during converting enzyme inhibition by teprotide

M. J. Vandenburg* M.R.C.P.
J. J. Morton† Ph.D.
G. H. Williams** M.D.
F. P. Marsh* F.R.C.P.

*Medical Unit and Department of Nephrology, The London Hospital, E1 1BB, †M.R.C. Blood Pressure Unit, Glasgow, and **Peter Bent Brigham Hospital, Boston, Mass.

Summary
Changes induced by i.v. and subcutaneous teprotide in plasma renin, angiotensin I, angiotensin II, aldosterone and bradykinin were studied in a renal transplant patient with severe high renin hypertension, before and after trinephrectomy. The immediate reduction in BP produced by teprotide was not solely attributable to the inhibition of conversion of angiotensin I to angiotensin II, because there was also a transient increase in serum bradykinin; however, the prolonged anti-hypertensive effect of teprotide appeared independent of bradykinin. After trinephrectomy, teprotide lowered systolic BP but had no significant effect on diastolic BP or plasma bradykinin. β-blockade prevented the secondary increase in plasma renin which followed teprotide, thereby potentiating its anti-hypertensive effect.

Introduction
Angiotensin I converting enzyme (ACE), a peptidylpeptide hydrolase also known as kininase II, converts angiotensin I (AI) to angiotensin II (AII) and degrades bradykinin (Yang, Erdos and Levin, 1971). Inhibition of these actions might be expected to reduce BP. The success has been reported of i.v. and subcutaneous teprotide, a parenteral ACE inhibitor, in reducing BP for 4 months in a woman who developed severe high renin hypertension after renal transplantation (VandenBurg et al., 1978). The authors now report changes in plasma renin, AI, AII, aldosterone and bradykinin concentrations produced by teprotide in the same patient, the effect of adding oxprenolol, and the results of i.v. teprotide after trinephrectomy (removal of the transplanted kidney as well as the patient’s own kidneys).

Method
The patient has been described previously (VandenBurg et al., 1978). Drugs were stopped 18 hr before each study except for frusemide, which was continued in a daily oral dose of 500 mg until trinephrectomy. The experiments were conducted after BP had become stable during run-in periods lasting one hr or more. Blood pressure measurements were made in the supine position, using an automatic recorder (arteriosonde Roche). Blood samples were drawn from a cannula inserted into a median cubital vein one hr before teprotide injection. Withdrawn blood was replaced by an equal volume of isotonic saline.

Plasma renin, AI, AII and aldosterone concentrations were measured by radio-immunoassay (Morton et al., 1976; Fraser, Guest and Young, 1973). Plasma bradykinin was assayed by a previously described modification of the method of Talamo, Hamer and Acroton (1969) (Williams and Hollenberg, 1977). Plasma concentrations of these hormones were measured at intervals varying from 30 min before to 12:5 hr after i.v. or subcutaneous teprotide. Five studies were conducted with the approval of the London Hospital Ethics Committee.

Study 1
Intravenous teprotide was administered in a dose of 0.25 mg/kg. Plasma renin and aldosterone were measured at −30, −15, +30, +60, +90 min.

Study 2
Intravenous teprotide was administered in a dose of 0.5 mg/kg. Plasma AI, AII, aldosterone and
bradykinin were measured at −30, −10, +10, +30, +120, +240 min.

Study 3

Subcutaneous teprotide was administered in a dose of 0·5 mg/kg. Plasma renin, AI, AII and aldosterone were measured at −20 min, +2, +3·5 and +9 hr.

Study 4

Intravenous teprotide was administered in a dose of 0·5 mg/kg; a further injection of 1·0 mg/kg was given at +2 hr. Oral oxprenolol 160 mg was administered at +3·5 hr. Plasma renin and aldosterone were measured at −15 min, +1, +5·5, +12·5 hr.

Study 5 (after trinephrectomy)

Teprotide was administered i.v. in a dose of 0·5 mg/kg. Plasma renin, AI, AII, aldosterone and bradykinin were measured at −30, −10, +10, +30, +120, +240 min.

Results

Study 1 (Fig. 1)

BP fell within 5 min of i.v. injection of teprotide (0·25 mg/kg) and had not returned to pre-injection levels after 4 hr. A marked decrease in plasma aldosterone and an elevation in renin were present from the time of the first post-injection measurement (30 min) to that of the last measurement (90 min).

Study 2 (Fig. 2)

BP fell within 5 min of the i.v. injection of teprotide (0·5 mg/kg) and was still normal after 4 hr. A marked decrease in AII, and an increase in AI, were noted from the time of the first post-injection measurement (10 min) to that of the last measurement (4 hr). Plasma aldosterone fell more slowly than AII. Plasma bradykinin was well above pre-injection levels at 10–30 min, but had returned to pre-injection levels at 2 hr.

Study 3 (Fig. 3)

Following the subcutaneous injection of 0·5 mg teprotide, BP did not change for over 2 hr, although AII and aldosterone concentrations had fallen and renin and AI had increased by this time. By 3·5 hr, there was a marked reduction in BP without further change in AII or aldosterone. The changes in these hormones were still present at 9 hr, although BP had risen towards pre-injection levels.

Study 4 (Fig. 4)

The rapid fall in BP produced by teprotide 0·5 mg/kg i.v. was not increased by a subsequent injection of 1 mg/kg; however, a further fall occurred within 40 min of a 160 mg oral dose of oxprenolol. This potentiation was associated with temporary reversal of the teprotide-induced hyperreninaemia. Plasma aldosterone was reduced at 1, 5 and 12 hr although BP was rising towards pre-injection levels.
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by the end of the study. Unfortunately, plasma taken for the measurement of AI and AII was lost.

Study 5 (Fig. 5)

Following teprotide 0.5 mg/kg given to the tri-nephrectomized patient systolic BP fell significantly during the first hour (P<0.02), and remained low for at least 6 hr. There was no significant change in diastolic BP. Plasma concentrations of renin, AI, AII and aldosterone were low throughout and showed no meaningful change after the injection; neither was there any significant change in bradykinin.

Discussion

It was found that teprotide inhibited ACE within 10 min of i.v. and 2 hr of subcutaneous injection. The effect was still marked 4 hr after i.v. and 9 hr after subcutaneous administration. The fall in BP which followed teprotide was associated with a reduction in plasma AII except after tri nephrectomy. The discrepancy between the time of onset of ACE inhibition and the fall in BP following subcutaneous injection in Study 3 suggests the possibility of another hypotensive mechanism which might involve bradykinin. But the effect on plasma bradykinin had

Fig. 2. The association of changes in blood pressure with alterations in plasma AI, AII, aldosterone and bradykinin concentrations after intravenous teprotide. Mean systolic and diastolic blood pressures during 12-min periods are illustrated, calculated from blood pressure readings made at intervals of up to 2 min.

Fig. 3. The association of changes in blood pressure with alterations in plasma renin, AI, AII and aldosterone concentrations after subcutaneous teprotide. Mean systolic and diastolic blood pressures during 30-min periods are illustrated, calculated from blood pressure readings made at intervals of up to 2 min.
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**FIG. 4.** The association of changes in blood pressure with alterations in plasma renin and aldosterone concentrations after intravenous teprotide, followed by oral oxprenolol. Mean systolic and diastolic blood pressures during 20-min periods are illustrated, calculated from blood pressure recordings made at intervals of up to 2 min.

**FIG. 5.** The association of changes in blood pressure with alterations in plasma renin, A1, AII, aldosterone and bradykinin after intravenous teprotide in the anephric patient. Mean systolic and diastolic blood pressures during 16-min periods are illustrated, calculated from blood pressure recordings made at intervals of up to 2 min.
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subsided within 2 hr of i.v. injection, and was of shorter duration than the alterations in BP and ACE activity. The hormonal effect of subcutaneous teprotide has not previously been demonstrated in man.

After trinephrectomy concentrations of plasma renin, AI, AII and aldosterone remained very low following teprotide, and there was no significant change in plasma bradykinin. Although diastolic BP did not change significantly there was a significant fall in systolic BP.

The relevance of changes in plasma bradykinin concentration to changes in BP produced by ACE inhibition is uncertain. Williams and Hollenberg (1977) showed a difference in response between salt-depleted hypertensive and salt-depleted normal subjects after injection of teprotide in a dose of 30 μg/kg; and increase in bradykinin concentration at 20 min was found in the hypertensive patients only. Mersey et al. (1977), from the same group, reported the same dose to cause a transient rise in bradykinin and reduction in BP in salt-depleted normal subjects; bradykinin and BP had returned to normal by 10 min although AII was still reduced. Sancho et al. (1976) were unable to demonstrate any increase in bradykinin in salt-deplete and replete normal subjects. More recent studies in humans have also been conflicting. Swartz et al. (1979) reported a rise in bradykinin at 20 min in a group of 20 salt-depleted patients with essential hypertension, but found evidence to suggest that the hypotensive effect was not mediated only by changes in plasma AII and bradykinin. Vinci et al. (1979) found no effect on plasma bradykinin in 13 salt-replete and deplete hypertensive patients, although they did find increased urinary kinin excretion which was greatest in those with the largest decrements in BP. This suggested the possibility of an effect mediated through an increase in local tissue levels of bradykinin. Miller et al. (1975) were unable to demonstrate any influence on bradykinin concentrations in one-kidney Goldblatt dogs although Nasjletti, Colina-Chourio and McGiff (1975) showed an effect. Johnston et al. (1979) found no increase in plasma bradykinin in essential hypertensive patients after 4, 8 and 12 weeks’ treatment with captopril, an orally active ACE-inhibitor. Using salt-depleted hypertensive rats Thurston and Swales (1978) showed a greater anti-hypertensive effect after teprotide than after saralasin. Blockade of the renin-angiotensin system with saralasin did not prevent a further fall in BP when teprotide was injected; they postulated that this additional anti-hypertensive action might be due to potentiation of bradykinin.

It was found that the anti-hypertensive effect of teprotide lasted much longer than the rise in plasma bradykinin which followed its injection. The authors cannot exclude the possibility that an increase in plasma bradykinin contributed to the early fall in BP, although the absence of a reciprocal increase in BP when bradykinin returned to pre-injection levels might suggest such an effect to be small. The results suggest that the increase in circulating bradykinin is unlikely to contribute to the more prolonged effect of teprotide on blood pressure.

It is uncertain why teprotide-induced changes in plasma AI and AII were more prolonged than the alterations in plasma bradykinin, although the enzyme which is inhibited is the same. It might be due to the greater affinity of ACE for bradykinin than for angiotensin I (Sofflar, 1976) or to the destruction of bradykinin by other proteases such as kininase I (Vinci et al., 1979). Increased degradation of bradykinin through other metabolic pathways (Erdos, 1975) might be responsible.

Following trinephrectomy, the effect of teprotide on plasma renin, AI, AII and bradykinin was abolished. Thurston and Swales (1978) have shown that the additional anti-hypertensive effect of teprotide after saralasin injection did not occur in binephrectomized rats, but was restored by infusion of small amounts of bradykinin. These results in humans and animals emphasize the importance of the kidney in the control of circulating bradykinin.

Although trinephrectomy abolished the effect of teprotide on diastolic BP, the authors were surprised to find a significant fall in systolic BP within 10-30 min which persisted for at least 4 hr. Man in 'T Veld et al. (1980) has described the production of orthostatic hypotension by captopril in fluid-depleted anephric haemodialysis patients, the effect being abolished by fluid repletion. Leslie et al. (1980) were unable to demonstrate any fall in BP in anephric patients given captopril 24 hr after haemodialysis.

The effect of the β-blocker oxprenolol in reducing teprotide-induced hyperreninaemia and increasing its hypotensive effect should be noted. The combination of a converting enzyme inhibitor and a β-blocker may be particularly potent.

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References


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