*Br. J. clin. Pharmac.* (1987), **23**, 88–90

# Effect of enalapril on the skin response to bradykinin in man

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We tested the effect of oral enalapril on intradermal bradykinin to determine if kininase II inhibition occurs with therapeutic doses *in vivo*. Six normal male volunteers took either 5 mg enalapril orally or placebo on 2 days. Three hours later bradykinin was injected into the skin of the back in doses increasing from $10^{-11}$ to $10^{-9}$ M. Enalapril increased the bradykinin-induced wheal. Inhibition of kininase II may cause accumulation of endogenous bradykinin. This could be an important mechanism in the occasionally reported side effect of angioedema with the angiotensin converting enzyme (ACE) inhibiting group of drugs.

**Keywords** enalapril bradykinin wheal and flare kininase II

## Introduction

Enalapril is an angiotensin converting enzyme inhibitor widely used in the treatment of cardiovascular disease (McFate Smith, 1984). However, recently it has been reported by the Committee on Safety of Medicines (1986) that 13 patients treated with enalapril have developed angioedema.

Bradykinin is formed in tissues undergoing trauma or allergic reaction (Regoli & Barabe, 1980; Wilhelm, 1971) and can cause inflammation vasodilatation and reduced vascular permeability (Oyvin *et al.*, 1972). Intradermal injection of bradykinin in man has been shown to cause wheal formation (Basran *et al.*, 1982). As bradykinin is inactivated in part by kininase II (ACE), inhibition of this enzyme may lead to tissue accumulation of bradykinin (Regoli & Barabe, 1980; Greenberg *et al.*, 1979). This accumulation of bradykinin might lead to cutaneous oedema in susceptible patients. We therefore studied the effect of oral administration of enalapril (5 mg) on intradermal injections of bradykinin in a double-blind, randomised study.

## Method

### *Subjects*

Six male normotensive healthy hospital personnel aged 32–42 years, weight 70–95 kg, gave informed consent to take part in the study. The protocol had the approval of the local hospital Ethics Committee.

### *Materials*

Enalapril 5 mg and matched placebo were prepared in capsules by the Pharmacy Department. Bradykinin (Sigma, Poole, UK) was dissolved in 100% ethanol for injection at a concentration of 1 mM before dilution in normal saline for injection in a 50 μl volume through a 27 gauge needle. The doses of bradykinin used were 10, 50, 100, 500 and 1000 pmol. The control was 0.2% ethanol in normal saline.

### *Protocol*

Each subject attended the Clinical Laboratory on two separate occasions following a light breakfast. Subjects took either 5 mg enalapril or placebo. Three hours later, injections of control and five doses of bradykinin were made intradermally into the skin of the back. The flare area was measured at 5 min by tracing around the area of flare on a perspex sheet. At 10 min the circumference of the wheal was drawn around with a biro and marked in and removed by sellotape. Areas of the wheal and flare were later measured by planimetry. The traces were drawn

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by the same independent observer on all occasions. The data were analysed by analysis of variance with Bonferroni's modification of Student's *t*-test (Wallenstein *et al.*, 1980).

## Results

No dose of bradykinin caused a flare significantly different in area from the control injection. Figure 1 shows the effect of bradykinin on wheal formation in the presence and absence of enalapril. On the placebo day bradykinin caused a dose-dependent increase in wheal from the control value of $0.88 \pm 0.2$ cm$^2$ to a maximum of $1.89 \pm 0.5$ cm$^2$ at 1000 pmol. After treatment with enalapril there was no difference in the control wheal, being $0.98 \pm 0.11$ cm$^2$. There was a larger wheal formation at all doses of bradykinin. The wheals after doses of 500 and 1000 pmol of bradykinin were significantly ($P < 0.05$) larger than on the enalapril day being $1.89 \pm 0.11$ and $3.0 \pm 1.0$ cm$^2$ with 1000 pmol of bradykinin on the placebo and enalapril days respectively.

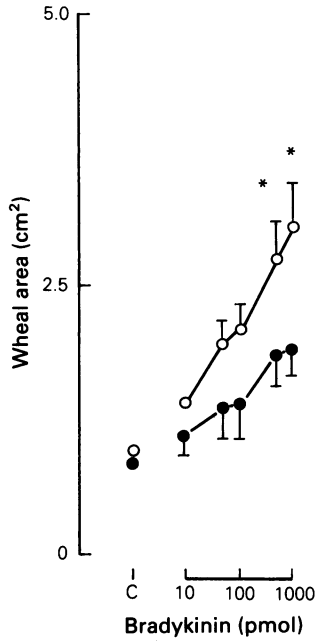


**Figure 1** Mean ± s.e. mean wheal area produced by control and increasing doses of bradykinin injected intradermally in six subjects receiving either oral placebo (●) or 5 mg of enalapril (○).
* significantly different from placebo ($P < 0.05$).

## Discussion

The study demonstrates that treatment with enalapril, at doses used in the treatment of hypertension (Enalapril in Hypertension Study Group, 1984) causes potentiation of cutaneous wheal formed by intradermal injections of bradykinin. These data are, therefore, compatible with the hypothesis that angioedema reported in patients on treatment with enalapril could indeed be caused by tissue accumulation of bradykinin. Rash has also been reported after treatment with enalapril and it is possible that increased dermal bradykinin may contribute to this in susceptible patients. However, this hypothesis requires that bradykinin is first formed within the tissues following minor trauma or an allergic reaction. Further work is, therefore, required in these patients to demonstrate the formation of bradykinin.

The work was supported by the Medical Research Council and Wellcome Trust.

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(*Received 23 June 1986, accepted 20 September 1986*)