The effect of indomethacin and enalapril on the cutaneous response to bradykinin

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The angiotensin converting enzyme inhibitors potentiate the wheal response to intradermal bradykinin. Both converting enzyme inhibitors and bradykinin stimulate prostaglandin synthesis and prostaglandins enhance the cutaneous response to bradykinin. We examined the possibility that the increased wheal response to intradermal bradykinin in the presence of enalapril was due to the effect of prostaglandins. Indomethacin did not inhibit the potentiation by enalapril of the wheal response to bradykinin.

Keywords enalapril indomethacin bradykinin wheal

Introduction

The angiotensin converting enzyme inhibitors are increasingly used in the management of cardiac failure and hypertension. Kininase II, an enzyme responsible for the degradation of bradykinin, is identical to angiotensin converting enzyme (Yang *et al.*, 1971) and is inhibited by captopril and enalapril. The cutaneous response to intradermal bradykinin is potentiated by converting enzyme inhibitors (Ferner *et al.*, 1987; Fuller *et al.*, 1987a). Prostaglandin synthesis is stimulated both by converting enzyme inhibitors (Zusman, 1981, 1984) and by bradykinin (Zusman, 1984; Zusman & Keiser, 1977; Heavey *et al.*, 1985); prostaglandins potentiate the tissue response to bradykinin (Basran *et al.*, 1982).

It has recently been shown that the wheal response to bradykinin is not dependent upon cyclooxygenase products (Crossman & Fuller, 1988); however, prostaglandins may yet be involved in the potentiation of the tissue response to bradykinin by converting enzyme inhibitors. To investigate the influence of prostaglandins on the interactive response between angiotensin converting enzyme inhibitors and bradykinin, we examined the effect of prostaglandin synthesis inhibition with indomethacin on the cutaneous response to intradermal bradykinin in the presence and absence of enalapril.

Methods

Six healthy volunteers took part in the study (five male; mean age 32 years). None had a history of peptic ulceration or hypertension and all had normal haematology and biochemistry profiles. All refrained from taking non-steroidal anti-inflammatory drugs or aspirin for 2 weeks before and throughout the study period. The protocol had the approval of the Western Infirmary Ethics Committee and written informed consent was obtained.

Indomethacin 75 mg, enalapril 10 mg and lactose placebo were prepared in identical capsules by the hospital pharmacy. Bradykinin (Sigma) was freshly dissolved in normal saline at concentrations of 10, 50 and 100 mg l⁻¹ (thus 0.1 ml volumes contained 1, 5 and 10 µg respectively) and kept on ice until used. Intradermal injections were made with a 25 g needle using a 0.22 µm in-line filter to sterilise the solutions. Twenty minutes after the intradermal injections, wheal area was measured by planimetry and skinfold thickness of the wheal measured using calipers.

Subjects attended for study on four occasions at 7 day intervals. On each study day, subjects took two study capsules (placebo + placebo; indomethacin 75 mg + placebo; enalapril 10 mg + placebo; indomethacin 75 mg + enalapril

Table 1 Mean (s.e. mean) wheal area (cm²) induced by intradermal bradykinin and change in blood pressure (mm Hg) 3 h after indomethacin 75 mg, enalapril 10 mg and the combination of both drugs

	Wheal area Bradykinin dose			Change in blood pressure	
	1 µg	5 µg	10 µg	Systolic	Diastolic
Placebo	0.29 (0.13)	0.91 (0.26)	1.78 (0.20)	0.8 (5.0)	1.7 (4.2)
Indomethacin	0.31 (0.09)	0.88 (0.15)	1.70 (0.30)	5.5 (1.7)	4.3 (0.6)
Enalapril	0.41 (0.20)	1.19 (0.11)	2.80 (0.22)*	1.2 (4.1)	-8.5 (4.1)†
Indomethacin + enalapril	0.54 (0.12)	1.70 (0.29)	3.40 (0.48)**	-0.8 (3.5)	-2.0 (2.1)

Significant findings: * $P < 0.05$ compared with placebo, ** $P < 0.01$ compared with placebo, † $P < 0.05$ compared with indomethacin.

10 mg in double-blind, random order) and the dose-response to intradermal bradykinin was measured 3 h later. Blood pressure (sitting) was recorded before taking the study capsules and immediately before the bradykinin injections.

Wheal areas on the 4 study days were compared at each bradykinin dose by two-way analysis of variance. Skinfold thickness and change in blood pressure were similarly compared by two-way analysis of variance.

Results

Table 1 shows the response to intradermal bradykinin and demonstrates the effect of indomethacin 75 mg, enalapril 10 mg and the combination of the two drugs on that response. Enalapril increased the wheal area to 10 µg bradykinin compared with placebo ($P < 0.05$); the difference at smaller bradykinin doses was not significant. Indomethacin did not affect the response to bradykinin compared with placebo nor was the response to a combination of enalapril and indomethacin significantly different from the effect of enalapril alone.

Skinfold thickness was not significantly altered by any of the treatments (data not shown). Enalapril reduced diastolic blood pressure compared with indomethacin ($P < 0.05$); the other treatments had no significant effect on blood pressure (Table 1).

Discussion

The angiotensin converting enzyme inhibitors were developed from the observation that

bradykinin potentiating activity from Brazilian snake venom also inhibited conversion of angiotensin I to angiotensin II (Ferreira, 1985). Thus it is not surprising that angiotensin converting enzyme inhibitors enhance the wheal response to intradermal bradykinin; our results confirm this and support the findings of other groups (Ferner *et al.*, 1987; Fuller *et al.*, 1987b).

We reasoned that indomethacin may antagonise the enhancement by converting enzyme inhibitors of the cutaneous response to bradykinin since prostaglandins act synergistically with bradykinin (Basran *et al.*, 1982) and prostaglandin synthesis in turn is increased by converting enzyme inhibitors (Zusman, 1981, 1984) and by bradykinin itself (Zusman, 1984; Zusman & Keiser, 1977; Heavey *et al.*, 1985). We failed, however, to show any effect of indomethacin on the response to bradykinin. This finding is unlikely to be due to insufficient cyclo-oxygenase inhibition as the timing and dose of indomethacin used in our study has been shown to reduce markedly prostaglandin synthesis (Vinge, 1985; Walenga *et al.*, 1986).

Prostaglandins, therefore, do not appear to play a role in potentiating the effect of converting-enzyme inhibitors on the immediate wheal response to intradermal bradykinin. If similar effects occur in the airways, then these findings would suggest that angiotensin converting enzyme inhibitor-induced cough and angio-oedema are not mediated by an interaction between bradykinin and cyclo-oxygenase products.

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