The effect of sulindac on dermal responses to bradykinin in normal subjects given an angiotensin converting enzyme inhibitor

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The ability of sulindac to modify the weal response to four doses of intradermal bradykinin in subjects given enalapril was tested in a double-blind cross-over study in normal volunteers. The dose-dependent increase in skin thickness after bradykinin was significantly reduced by prior administration of sulindac. Certain of the actions and adverse effects of angiotensin converting enzyme inhibitors may be due to the interaction of prostaglandins and bradykinin.

Keywords sulindac bradykinin angiotensin converting enzyme inhibitor

Introduction

It is known that angiotensin converting enzyme (ACE) inhibitors enhance the tissue effects of bradykinin (Ferner *et al.*, 1987, 1989), and that inhaled bradykinin causes cough and chest tightness (Fuller *et al.*, 1987). The accumulation of bradykinin is therefore a possible mechanism by which ACE inhibitors could cause the dry cough which occurs in a substantial proportion of patients (Yeo & Ramsay, 1989). The observation that sulindac, a non-steroidal anti-inflammatory drug, alleviates cough associated with ACE inhibitors (Nicholls & Gilchrist, 1987) has now been confirmed by a controlled trial (Choudry *et al.*, 1989).

To test the hypothesis that sulindac directly or indirectly modifies responses to bradykinin in subjects given ACE inhibitors, we undertook a double-blind placebo-controlled cross-over study of the effects of sulindac on bradykinin-induced dermal weals in normal volunteers given a single dose of enalapril.

Methods

The subjects were 10 healthy young men, aged 21–32 years. None had a history of drug allergy, and none was regularly taking any medicines. All gave written consent to the study, which was approved by the Joint Ethics Committee of the

Newcastle Health Authority and the University of Newcastle upon Tyne.

Each subject was studied twice, in random order. On one occasion he received a dose of sulindac 200 mg, at 16 h before, and again at 4 h before injection. On the other occasion, matched tablets containing lactose as placebo were given. Two hours before injection on each occasion, subjects received enalapril 10 mg orally. At 11.00 h, 100 µl injections of 0.9% sodium chloride solution containing 0, 1.5, 3, 6, and 12 µg of bradykinin were given intradermally at 5 min intervals, and then increase in skin thickness due to bradykinin was measured with modified Harpenden callipers, as previously described (Ferner *et al.*, 1989). Subjects were also observed for facial flushing (Ferner *et al.*, 1987).

Results are quoted as mean $\pm$ s.e. mean. The effects of different doses of bradykinin and of sulindac on bradykinin dose-response were assessed by two-way analysis of variance with correction for repeated measures, using the program BMDP2V (Biomedical Data Program Statistical Software Inc, Los Angeles, California). Although logarithmic transformation of responses improved the heteroscedasticity, it did not alter conclusions, and so calculations on untransformed data are presented. Values of $P < 0.05$ were taken to be statistically significant.

Figure 1 The increase in skin thickness (mm) due to bradykinin vs the dose of bradykinin (μg) given intradermally to 10 normal men after two doses of placebo ($\square$) or sulindac 200 mg ($\blacklozenge$) and one dose of enalapril 10 mg. Bars indicate the s.e. mean.

Results

The weal responses to different doses of bradykinin in the absence and presence of sulindac are shown in Figure 1. There was a marked effect of dose on mean response ($F_{3,27} = 55.6$, $P < 0.0001$). The mean response over all four doses was reduced from 2.1 mm to 1.6 mm ($F_{1,9} = 5.3$, $P = 0.047$) in the presence of sulindac. There was no indication of an interaction between treatment and bradykinin dose ($F_{3,27} = 0.06$, adjusted $P = 0.94$).

Flushing was observed in six of 12 subjects 2–3 min after the intradermal injection of 12 μg of bradykinin, irrespective of whether they had been pretreated with sulindac or placebo. One subject flushed after the administration of bradykinin on the placebo day but not on the sulindac day.

Discussion

Tissue effects of bradykinin are increased in normal subjects and in hypertensive patients given ACE inhibitors (Ferner *et al.*, 1987, 1989). In this study, the prostaglandin synthetase

inhibitor sulindac reduced weal responses to bradykinin by about 25% in the normal volunteers 2 h after enalapril. This might have been due to a nonspecific reduction in inflammatory response, to a specific action of sulindac on bradykinin, or to a specific reduction in the ACE inhibitor induced potentiation of bradykinin responses. Exogenous prostaglandins, notably PGE_2 and PGI_2 , potentiate the inflammatory actions of intradermal bradykinin in the rabbit (Williams, 1979). Bradykinin itself stimulates the release of PGI_2 from endothelium *in vivo*, and this effect can be inhibited by aspirin (Heavey *et al.*, 1985). However, a mixture of bradykinin and indomethacin produced the same inflammatory reaction as bradykinin alone when injected intradermally (Williams, 1979). Previous studies have failed to find an effect of non-steroidal anti-inflammatory drugs on skin responses to bradykinin in man, in the absence of ACE inhibitors (Crossman & Fuller, 1988; McAlpine & Thomson, 1989). A single dose of indomethacin did not alter responses to bradykinin injected 3 h after oral enalapril (McAlpine & Thomson, 1989). The difference from the present study might be due to the small number of subjects or to the difference in time between enalapril and bradykinin administration: tissue effects of ACE inhibitors seem to be maximal by 2 h (Ferner *et al.*, 1987). It is also possible that sulindac possesses properties in addition to its direct effect on prostaglandin synthesis. Our study, however, is consistent with the hypothesis that interaction between kinins and prostaglandins is responsible for the enhancement of skin responses by ACE inhibitors.

We failed to demonstrate suppression of the transient facial flushing which is seen after high doses of intradermal bradykinin in subjects receiving ACE inhibitors. This could have been due to insensitivity of the method for assessing flushing (simple observation) or because the transient vasodilatory effects of bradykinin are dissociated from its action on vascular permeability.

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