Effect of sulindac on the cough reflex of healthy subjects

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The effects of a single dose of sulindac 200 mg and placebo on the capsaicin-induced cough reflex were studied in a two-phase double-blind crossover study in 18 healthy subjects. Sulindac increased the threshold for capsaicin cough response significantly, but did not alter D5, peak response, or the total cough response when compared with placebo values.

Keywords sulindac cough reflex

Introduction

Evidence that the non-steroidal anti-inflammatory drug sulindac may influence the cough reflex has emerged from investigation of the persistent dry cough which commonly complicates treatment with angiotensin converting enzyme (ACE) inhibitors (Berkin & Ball, 1988; Fuller, 1989; Just, 1989; Yeo & Ramsay, 1990). Uncontrolled observations (Nicholls & Gilchrist, 1987) and two controlled studies (Choudry *et al.*, 1988; Gilchrist *et al.*, 1989) suggested that sulindac might improve ACE inhibitor-induced cough, and Choudry *et al.* (1988) also showed that sulindac had a significant effect on the capsaicin-induced cough reflex in patients with this side-effect. The effect of sulindac on capsaicin cough appeared specific to those with ACE inhibitor-induced cough, as it had no effect in patients with dry cough of other causes (Fuller *et al.*, 1989). However there is reason to believe that sulindac could have some effect on the capsaicin-induced cough reflex in healthy subjects. Choudry *et al.* (1989) have shown that inhaled prostaglandin E₂ increased the cough response to high doses of capsaicin, although it had no effect upon the threshold for cough. One might anticipate that a prostaglandin synthetase inhibitor such as sulindac would have an opposing action. For this reason we have examined the effect of sulindac on the cough response to capsaicin in healthy subjects.

Methods

Eighteen healthy subjects (nine men, nine women; aged 21–46 years) who had no contraindication to sulindac, and had taken no prostaglandin synthetase inhibitor for 14 days, consented to a double-blind balanced two-phase crossover study comparing a single oral dose of sulindac 200 mg with placebo. The study was approved by the hospital ethics committee. The two treatment phases were separated by 1 week. The cough reflex was examined 4 h after dosing with placebo or sulindac 200 mg. This

was done by administering in random order, via DeVilbiss No 40 nebulisers, single inhalations of normal saline or capsaicin in nine log incremental doses from 0.025–6.25 nmol. Capsaicin was prepared as a solution in normal saline. The response to capsaicin was measured as the number of coughs in 1 min after each dose. The responses to capsaicin after sulindac and placebo were compared by examining the threshold (lowest dose to cause cough); D5 (dose required to cause 5 coughs/min); peak cough response; and the total cough response (sum of cough at all doses). Analysis appropriate to the two-period crossover design was used (Hills & Armitage, 1979), and showed no significant treatment-period interaction. Direct comparisons of the two treatments for threshold and D5 were made using the nonparametric sign test, and mean doses of capsaicin cited are calculated as geometric means.

Results

Two of the 18 subjects could not tolerate the higher doses of capsaicin. The mean dose-response curves for capsaicin after treatment with sulindac and placebo for the 16 subjects who could tolerate all doses are shown in Figure 1. Sulindac had no obvious effect on the overall dose-response curve. This was also true when the capsaicin dose-response curve up to 0.78 nmol, a dose tolerated by all 18 subjects, was examined (data not shown). However the threshold for cough in response to capsaicin was increased significantly after sulindac (Figure 2). Thirteen of 18 subjects required an increased dose of capsaicin to elicit cough after sulindac, compared with 4 of 18 after placebo ($P < 0.05$; Figure 2). There was no difference between sulindac and placebo treatment as regards D5 (placebo 1.67 nmol, sulindac 1.97 nmol), peak response (placebo 7.1 coughs/min, sulindac 8.4 coughs/min), or the total response to all doses of capsaicin (placebo 22.4

Figure 1 Log dose-response curves for capsaicin-induced cough after treatment with sulindac 200 mg (■) or placebo (□) in 16 subjects who could tolerate all doses of capsaicin.

coughs, sulindac 23.6 coughs). The mean (and 95% CI) difference between sulindac and placebo in total cough response to capsaicin was +1.2 (−2.7 to +5.0) coughs, with the lower confidence interval indicating that sulindac is unlikely to reduce total cough by more than 12% from placebo values.

Discussion

The effect of sulindac on the cough response to capsaicin has been examined in patients with cough caused by ACE inhibitors and other conditions (Fuller *et al.*, 1989) but not to our knowledge in healthy subjects. In the present study a single dose of sulindac 200 mg taken 4 h before cough challenge with capsaicin significantly raised the cough threshold. It had no other important effect on the dose-response to capsaicin, with no difference between sulindac and placebo as regards D5, peak response, or total cough response. The study had sufficient power to exclude a large effect on the total cough response, as the 95% confidence intervals indicated that sulindac was unlikely to reduce total cough by more than 12%.

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Figure 2 Threshold dose of capsaicin (lowest dose causing cough) in 18 subjects after treatment with placebo (hatched bars) and sulindac 200 mg (solid bars). The threshold for subject one after placebo treatment was zero.

The effect of sulindac seen in this study was not anticipated from previous work. In patients with ACE inhibitor-induced cough the main effects of sulindac reported were significant increases in D2 and D5 for capsaicin (Choudry *et al.*, 1988). These parameters of the capsaicin dose-response curve were not influenced by sulindac in the present study. In healthy subjects inhalation of prostaglandin E₂ enhanced the response to high doses of capsaicin, but had no effect on the threshold for cough (Choudry *et al.*, 1989). One might have expected the opposite effect with sulindac, but in the event it altered the threshold significantly and had no influence upon the response to higher doses of capsaicin.

The effect of sulindac observed in this study suggests that prostaglandins may have some role in the cough reflex in healthy subjects. It suggests also that the response to sulindac in ACE inhibitor-induced cough may not be specific to that condition, although Fuller *et al.* (1989) observed no effect of sulindac in patients with cough of other causes. The effect of sulindac on the cough reflex was small in the present study, and this may explain the somewhat inconsistent results in previous studies of sulindac in ACE inhibitor-induced cough (Choudry *et al.*, 1988; Gilchrist *et al.*, 1989).

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