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Differences in the mode of cough augmentation by four angiotensin-converting enzyme inhibitors in guinea-pigs

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Abstract—The effects of four angiotensin-converting enzyme (ACE) inhibitors, captopril, enalapril, quinapril and alacepril, on the cough responses caused by citric acid and capsaicin inhalation were studied in normal and bronchitic guinea-pigs. After an oral dose of 10 mg kg^{-1}, none of the ACE inhibitors had an effect on the citric acid-induced coughing response in normal guinea-pigs. Enalapril 10 mg kg^{-1} significantly increased the number of coughs caused by capsaicin inhalation. In bronchitic guinea-pigs, 10 mg kg^{-1} captopril and enalapril significantly increased the number of capsaicin-induced coughs. When administered daily for 8 days, captopril was the only ACE inhibitor which significantly increased the number of coughs due to citric acid inhalation. The present results indicate that the ACE inhibitors had different modes of cough augmentation.

Although angiotensin-converting enzyme (ACE) inhibitors, have been widely used during the past decade for treatment of hypertension and congestive heart failure, persistent dry cough has recently been identified as an adverse side effect (Seseko & Kaneko 1985; Israel-Biet et al 1986; Semple & Herd 1986; Webb et al 1986; Coulter & Edwards 1987), which is reversible, when the drug is discontinued.

The incidence of cough production appears to differ among ACE inhibitors, being between 1 and 15% (Strumpe et al 1984; Coulter & Edwards 1987; Hood et al 1987). Thus, it would be important for facilitating development of new ACE inhibitors to know whether the cough production is associated essentially with ACE inhibitors or not, and whether the mode of cough production is the same or different among ACE inhibitors developed so far. Because ACE inhibitors themselves do not produce cough responses in experimental animals, the effects of four ACE inhibitors (Fig. 1) on the cough responses caused by various cough inducers were studied.

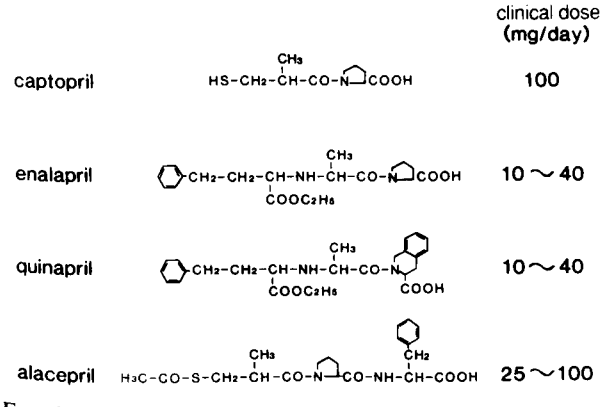

FIG. 1. Chemical structures and clinical daily doses of four angiotensin-converting enzyme inhibitors.

Materials and methods

Experimental animals. Male Hartley strain guinea-pigs, 300–350 g, were used in all experiments. Bronchitic guinea-pigs were prepared by exposure to 200 ppm SO_2 gas for 2 h day^{-1} for 7 days. Sulphur dioxide exposure was carried out using the apparatus described previously (Kasé et al 1982; Miyata et al 1987). The guinea-pigs exposed to SO_2 gas under the above conditions showed bronchitis characterized by an increase in the number of the inflammatory cells in broncho-alveolar lavage fluid, an increase in the sensitivity of the bronchial smooth muscle to acetylcholine and histamine, and a reduction of neutral-endopeptidase (NEP) activity in the trachea (Fuchikami 1992). A few of the animals used sometimes coughed during SO_2 exposure but did not cough spontaneously after termination of the exposure period. A group consisting of 8–10 animals was used for each dose of drug.

Cough production and recordings. Non-anaesthetized animals were placed individually in an acryl-resin plethysmograph which consisted of a head chamber (1177·5 cm^3) and a body chamber (1177·5 cm^3), and were forced to inhale 0·1 M (or 0·05 M) citric acid or 10^{-13} M (or 10^{-14} M) capsaicin solution for 2 min using an ultrasonic nebulizer (MEP-1100, Nihon Kohden), connected to the head chamber and adjusted to 0·2 mL min^{-1}. Coughing was monitored and recorded on a pen recorder through a flow meter (TUR-3200, Nihon Kohden). The sound of coughing was also monitored through a small microphone placed within the plethysmograph and recorded on a tape recorder. The animals were continuously observed by a trained and uninformed observer during the experiment. Coughing could be easily distinguished from sneezing, since there was a clear difference between the two in sound as well as in behaviour of the animals. The number of coughs during a 2-min inhalation period and the subsequent 13 min, was counted. Each ACE inhibitor was given orally 4 h after the experiment for pre-administration control, and 30 min later, the animal was re-challenged with one of the cough inducers. In the multiple-dose experiment, cough production was confirmed before the first dose, as described above, and the number of coughs was taken as the pre-administration control value. Dosing was carried out for 8 days. Thirty minutes after the final dose, the animals were again tested for cough production. The effect was evaluated as an increase or a decrease in the number of coughs; the number of coughs before and after drug administration was statistically compared using Student's *t*-test.

Drug administration. ACE inhibitors, suspended in 0·5% carmellose sodium solution, were administered orally at a dose of 10 mg kg^{-1} unless otherwise noted. Before administration, the animals were fasted for 8 h, but had free access to drinking water. Capsaicin was dissolved in 10% ethanol and 10% Tween 80 and then diluted in saline before use. Citric acid was dissolved in distilled water.

Results

Single doses of ACE inhibitors did not increase the cough response in normal guinea-pigs, induced by citric acid (Table 1). The number of capsaicin-induced coughs was significantly increased by enalapril but not by other ACE inhibitors (Table 1). Chronic dosing with captopril significantly increased the

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Table 1. Effects of single administration of ACE inhibitors on coughing induced with citric acid or capsaicin in normal guinea-pigs. Values are the numbers of coughs in the 15-min test period.

ACE inhibitor	Dose (mg kg^{-1})	Citric acid		Capsaicin	
		Before	2 h	Before	2 h
Control	—	4·3 ± 1·5	3·7 ± 1·1	3·7 ± 0·7	5·3 ± 1·0
Captopril	10	5·0 ± 0·7	5·3 ± 1·1	2·7 ± 0·09	3·8 ± 2·0
Enalapril	5	3·5 ± 1·2	4·8 ± 1·8	2·5 ± 0·4	3·3 ± 1·7
	10	5·3 ± 0·7	7·0 ± 1·7	2·9 ± 0·5	7·3 ± 1·6*
Quinapril	10	4·4 ± 0·8	4·0 ± 0·9	2·5 ± 1·0	3·4 ± 1·1
Alacepril	10	4·9 ± 0·5	5·1 ± 1·0	2·5 ± 0·7	2·7 ± 0·5

Each value is the mean ± s.e.m. of 8–10 animals. *$P < 0.05$ compared with the value before the dose of ACE inhibitor.

Table 2. Effects of chronic administration of ACE inhibitors on coughing induced with citric acid or capsaicin in normal guinea-pigs. Values are the numbers of coughs in the 15-min test period.

ACE inhibitor	Dose (mg kg^{-1})	Citric acid		Capsaicin	
		Before	8 days	Before	8 days
Control	—	4·0 ± 2·0	6·0 ± 1·7	4·8 ± 2·2	2·0 ± 0·6
Captopril	10	2·8 ± 1·0	7·6 ± 1·3*	4·6 ± 1·1	8·2 ± 1·8
Enalapril	10	3·0 ± 1·1	4·8 ± 1·7	4·0 ± 0·7	3·0 ± 1·1
Quinapril	10	4·0 ± 0·6	1·8 ± 0·5	3·8 ± 1·5	1·7 ± 0·7
Alacepril	10	3·8 ± 1·3	4·2 ± 1·0	3·0 ± 1·2	2·8 ± 0·6

Each value is the mean ± s.e.m. of 8–10 animals. *$P < 0.05$ compared with the value before the dose of ACE inhibitor.

Table 3. Effects of single administration of ACE inhibitors on coughing in bronchitic guinea-pigs induced with citric acid or capsaicin. Values are the numbers of coughs in the 15-min test period.

ACE inhibitor	Dose (mg kg^{-1})	Citric acid		Capsaicin	
		Before	2 h	Before	2 h
Control	—	2·3 ± 1·2	3·3 ± 1·3	1·4 ± 0·5	3·4 ± 0·6
Captopril	10	2·6 ± 0·8	7·0 ± 2·4	2·8 ± 1·3	7·0 ± 0·8*
Enalapril	5	1·7 ± 0·5	3·0 ± 1·2	2·6 ± 0·4	5·4 ± 0·2*
	10	2·2 ± 1·1	8·2 ± 2·9	1·2 ± 0·2	6·4 ± 0·9*
Quinapril	10	2·8 ± 0·7	3·8 ± 1·0	2·5 ± 1·3	5·2 ± 2·6
Alacepril	10	2·6 ± 1·0	6·6 ± 1·8	2·4 ± 0·2	3·0 ± 0·5

Each value is the mean ± s.e.m. of 8–10 animals. *$P < 0.05$ compared with the value before the dose of ACE inhibitor.

number of coughs in normal animals induced with citric acid (Table 2).

Cough responses were produced by a lower concentration of cough inducers in bronchitic animals compared with normal animals. A single dose of ACE inhibitor did not produce significant increases in the number of citric acid-induced coughs. However, captopril and enalapril significantly increased the number of coughs due to capsaicin, but quinapril and alacepril had no significant effect (Table 3).

Discussion

Enalapril augmented the coughs in normal and bronchitic guinea-pigs induced by capsaicin but not by citric acid. Capsaicin releases substance P from the afferent C-fibre of the cough reflex arc to stimulate cough. Citric acid, however, appears to stimulate mainly the A-fibre terminal to produce cough, as inhaled local-anaesthetics, which paralyse the C-fibre, more strongly depressed the coughs caused by capsaicin than those caused by citric acid (Choudry et al 1990). Because ACE degrades neuropeptides such as substance P and bradykinin (Cascieri et al 1984; Yokosawa et al 1985; Skidgel & Erdos 1987), ACE inhibitors should increase the level of such neuropeptides in the airway. Therefore, the difference in the site of action for cough production between the two cough inducers may account for the present result.

In bronchitic animals, 5 mg kg^{-1} enalapril or 10 mg kg^{-1} captopril also augmented the capsaicin-induced cough response. The level of NEP, a degrading enzyme of substance P, decreases in bronchitic guinea-pigs (Fuchikami et al 1991). Our preliminary study revealed that inhalation of phosphoramidon, a NEP inhibitor, caused coughs in normal guinea-pigs. Therefore, a reduction in the NEP activities of the airway in bronchitic animals, not determined in the present study, might explain the above results.

Alacepril did not increase the number of coughs in spite of being a prodrug of captopril. Takeyama et al (1985a) have reported that 10 mg kg^{-1} alacepril, administered orally, showed

an anti-hypertensive action more potent than or comparable with that of the same dose of captopril in hypertensive animal models. Thus, it seems unlikely that the difference in the augmentation attributes to the bioavailability of each ACE inhibitor. Orally-administered alacepril was metabolized to disulphides and captopril through desacetyl-alacepril (Matsumoto et al 1986). Desacetyl-alacepril has been reported to inhibit the noradrenaline-induced vasoconstrictive response, the action being more potent than that of alacepril (Takeyama et al 1985b). This finding indicates that alacepril is not a simple prodrug of captopril. Further studies are needed to clarify the mechanism of the difference in cough augmentation between alacepril and captopril.

A single dose of enalapril augmented the capsaicin- and citric acid-induced cough response, but chronic dosing had no effect. On the other hand, captopril augmented citric acid-induced coughing following chronic dosing but not after single dosing. It seems unlikely that the difference between the two types of dosing come from the bioavailability of each ACE inhibitor, as there was no significant difference in C_{max}, t_{max} and $t_{\frac{1}{2}}$ between single and chronic dosing of enalapril (Nakashima et al 1984). Furthermore, it has been reported that 10 mg kg^{-1} enalapril produced a progressive fall in blood pressure with a peak on the 7th day of chronic dosing (Oomura et al 1985). On the other hand, the same dose of captopril produced the maximal hypertensive effect on the 4th day of chronic dosing and the effect gradually reduced in spite of further dosing (Oomura et al 1985). Our preliminary study revealed that 10 mg kg^{-1} enalapril increased the level of angiotensin in the lung of guinea-pigs compared with that of 10 mg kg^{-1} captopril. Because ACE degrades not only angiotensin but also substance P and bradykinin (Cascieri et al 1984; Yokosawa et al 1985), a possible explanation for this is that chronic dosing of enalapril caused desensitization of the afferent fibre of the cough reflex to cough inducers such as substance P. The result of chronic dosing of captopril needs further study to clarify the mechanism.

Quinapril, captopril and enalapril were kind gifts from Yoshitomi Pharmaceutical Co. Ltd (Japan) and alacepril from Dainippon Pharmaceutical Co. Ltd (Japan).

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