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The effect of nedocromil sodium, sodium cromoglycate and codeine phosphate on citric acid-induced cough in dogs

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1 The effects of nedocromil sodium, sodium cromoglycate and codeine phosphate on citric acid-induced cough have been studied in conscious tracheostomised dogs.

2 Nedocromil sodium (approximately 15 mg given as an aerosol) and codeine phosphate (5 mg kg^{-1}, i.v.) significantly increased the time to the first cough when dogs were challenged with citric acid aerosol. The mean number of coughs in the initial period of coughing fell after treatment of dogs with nedocromil sodium or with codeine phosphate, but this reduction in mean cough number was not statistically significant.

3 Neither sodium cromoglycate (approximately 15 mg given as an aerosol) nor saline had significant effect on a citric acid challenge.

4 It is concluded that nedocromil sodium, but not sodium cromoglycate, possesses an anti-tussive action that may result from inhibition of sensory nerve activity in the lung. Nedocromil sodium may prove useful in the treatment of unproductive cough in situations where the use of a centrally-acting antitussive is undesirable.

Introduction

Cough is a powerful and useful physiological mechanism which allows the airways to be cleared of foreign material and excess secretions. Although it would be dangerous to suppress cough indiscriminately there are many situations in which cough does not serve any useful purpose. The present treatment of cough involves the use of centrally acting drugs based on opioid analgesics which can have unpleasant side effects (Eddy *et al.*, 1969; Salem & Aviado, 1970). Attempts to discover a peripherally acting cough suppressant have generally been unsuccessful and have been based on a local anaesthetic action (Dain *et al.*, 1975; Cross *et al.*, 1976; Kandus & Utrata, 1976).

Nedocromil sodium is a new drug for the treatment of reversible obstructive airway disease which prevents the release of mediators from both mucosal and connective tissue mast cells (Eady *et al.*, 1985; Holgate, 1986). Routine testing of this compound in a variety of respiratory models suggested the presence of a peripheral anti-tussive action and experiments to evaluate this further by use of citric acid-induced cough in the conscious dog are described in this paper. Sodium cromoglycate (an agent with some actions that resemble those of nedocromil sodium) and the standard cough suppressant, codeine phosphate, were used for comparative purposes.

Methods

One female and three male Beagle dogs weighing approximately 14 kg were used in this study. The animals were selected for their good nature and their willingness to sit or stand quietly for several hours in a laboratory. Two months prior to the experiment a permanent tracheostomy was made in each dog according to the method of Slatter (1985). The dogs were then trained to accept a tracheostomy tube (Portex 7 mm) which was left in place for the experiment.

With the tracheostomy tube in place, the dogs were challenged with an aerosol of 1% citric acid generated by an ultrasonic nebuliser (Mistogen EN 145). The aerosol was directed over the end of the tracheostomy tube through wide bore (22 mm) corrugated tubing. The time taken for the dog to start

coughing and the number of coughs produced were recorded. As soon as coughing started the citric acid aerosol was stopped. Citric acid challenges were made every 30 min until two consecutive challenges produced coughing within a minute and within a time not differing by more than 20 s. This occurred usually on the second and third challenges. Twenty minutes before the next challenge the dogs were treated via the tracheostomy with an aerosol generated from either saline (0.9%), sodium cromoglycate (2%), or nedocromil sodium (2%) or they were given codeine phosphate (5 mg kg^{-1}, i.v.). Nedocromil sodium and sodium cromoglycate solutions were prepared in 0.9% saline. The aerosols were generated by an ultrasonic nebuliser (Mistogen EN 145) and inhaled by the dogs for 5 min. Calculations based on the output of the nebuliser, the tidal volume and the respiratory rate of the dogs showed that a dose of approximately 15 mg of drug was delivered to the lung. After drug administration three more citric acid challenges were performed. Citric acid was not administered for a period exceeding 2 min.

Each dog received each treatment in different sequences and on separate weeks.

Statistical analysis

Student's *t* test for paired values was used to test for significance. Differences that produced *P* values of less than 0.05 were accepted as significant.

Results

Inhalation of an aerosol of citric acid caused coughing within 1 min in all four dogs and each dog produced between 1 and 10 coughs per challenge. The time to the first cough response to citric acid was consistent over a 2 h period when the challenges were given every 30 min.

Nedocromil sodium and codeine phosphate significantly prolonged the time to the first cough but in the second dosage used, codeine phosphate was longer acting. Neither saline nor sodium cromoglycate had any effect on time to first cough (Figure 1). For all treatment groups (including the saline group), the mean number of coughs observed in response to the citric acid challenge made 20 min after treatment was smaller than that observed in response to the challenge made 10 min before treatment (pre-nedocromil sodium 3.5 ± 1.6, post-nedocromil sodium 1.25 ± 1.25; pre-codeine phosphate 5.7 ± 1.8, post-codeine phosphate 0.75 ± 0.45; pre-saline 4.5 ± 0.8, post-saline 4.0 ± 1.4; pre-sodium cromoglycate 3.7 ± 0.8, post-sodium cromoglycate 3.0 ± 1.3; mean $\pm$ s.e. mean). While this reduction appeared greatest in the case of nedocromil sodium and codeine phosphate, in no treatment group did the difference between pre- and post-treatment mean values reach the level of statistical significance. This may have been a reflection of the large variation in the number of coughs produced by each challenge.

Discussion

Inhalation of an aerosol of citric acid induced coughing in tracheostomised dogs. When citric acid challenges were given every 30 min the time to the first cough measured from the start of the challenge was consistent for each dog, although the number of coughs produced by the challenge was variable.

Many methods, using conscious and anaesthetized animals, have been used to assess anti-tussive activity (Bucher, 1958). The main problem with these methods is the variability of the response in conscious animals, and the depression of the cough reflex in anaesthetized models resulting in high thresholds to cough. The model described here proved to be reliable and sensitive if the time to the first cough was used as the prime measurement. The variability normally associated with conscious models may have been reduced by delivering the irritant stimulus direct to the lungs via a tracheostomy.

The cough produced by inhalation of citric acid probably resulted from the direct or indirect stimulation of 'lung irritant' or 'cough' receptors (Widdicombe, 1954). In anaesthetized dogs with hyperreactive airways, citric acid has been shown to cause reflex bronchoconstriction (Hirshman *et. al.*, 1983) although no coughing was reported, possibly because autonomic reflexes were depressed by anaesthesia. It is possible that in our experiments coughing was secondary to bronchoconstriction but as lung mechanics were not measured, this cannot be established. In man, citric acid aerosol produces coughing and this is thought to be the result of stimulation of 'cough' receptors rather than a secondary response to bronchoconstriction (Bickerman & Barach, 1954).

Codeine phosphate and nedocromil sodium significantly increased the time to the first cough. The protective action of nedocromil sodium lasted for about 30 min and that of codeine phosphate for longer than 1 h. In contrast neither sodium cromoglycate nor saline had any effect on the response to citric acid.

Codeine phosphate suppresses cough by an action on the central nervous system (CNS) (May & Widdicombe, 1954). The mechanism of action of nedocromil sodium is unknown. The drug is not a conventional bronchodilator (Eady *et al.*, 1985) and it does not penetrate the CNS (Dr D. Smith, Fisons plc, Research and Development Laboratories, per-

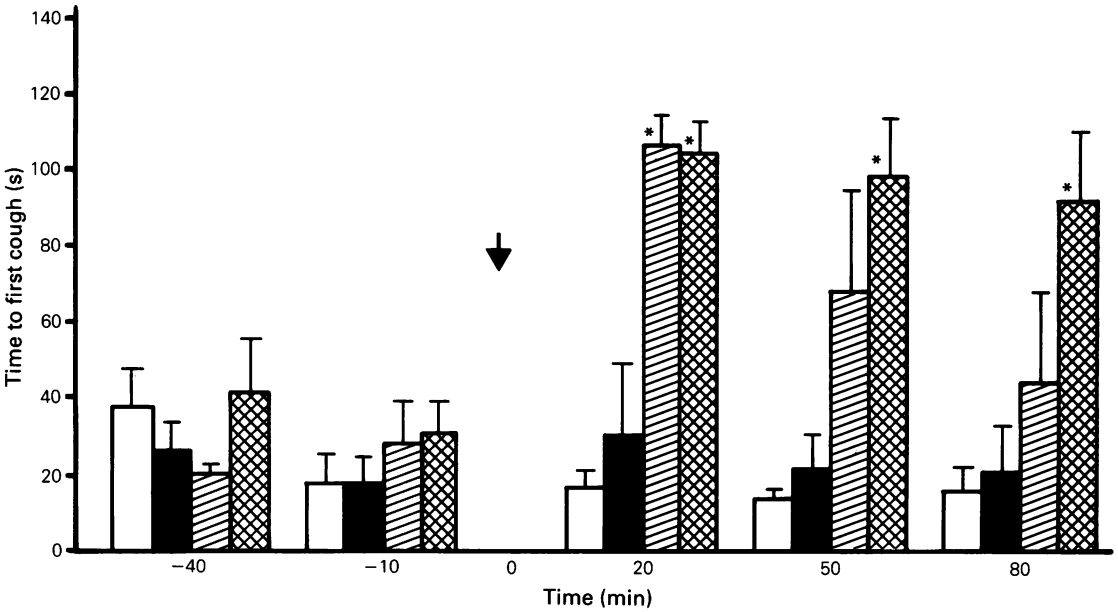

Figure 1 The effect of aerosols of saline (open columns); 2% sodium cromoglycate to a total dose of 15 mg (solid columns); 2% nedocromil sodium to a total dose of 15 mg (hatched columns); and codeine phosphate 5 mg kg^{-1}, i.v. (cross-hatched columns) on the time to the first cough following citric acid challenge in tracheostomised dogs. Drugs were given at arrow. Values are with mean s.e. mean shown by vertical lines, $n = 4$; * $P < 0.05$ (tested against the control value measured 10 min before drug treatment).

sonal communication). A possible explanation of its anti-tussive action is that it suppresses or protects the lung 'irritant' or 'cough' receptors, making them refractory to the actions of citric acid.

Experiments have been reported where the anti-tussive effects of drugs given by aerosol, and which, therefore were assumed to have a peripheral action, were tested. Most of these studies have been with drugs which are established local anaesthetics and they have been examined in anaesthetized animals or patients. Dain *et al.* (1975) inhibited a mechanically evoked cough from the trachea and carina of anaesthetized dogs and rabbits with an aerosol of 5% bupivacaine hydrochloride. Cross *et al.* (1976) obtained a similar effect with bupivacaine in anaesthetized dogs and in unanaesthetized man. Kandus & Utrata (1976) depressed coughing in patients with chronic non-specific bronchopulmonary diseases using Thiameton Spofa administered by inhalation. Korpas *et al.* (1978) suppressed mechanically induced cough in anaesthetized cats with RM 20201, a drug thought to act on sensory receptors (Langrehr, 1963) although the drug is known to have an action in the CNS (Jaffe & Martin, 1985).

Nedocromil sodium, but not sodium cromoglycate, possesses an anti-tussive action which might result from suppression of sensory nerve activity in the lung. The type of sensory nerve affected by nedocromil sodium is not known. Nedocromil sodium may be useful in the treatment of unproductive cough in situations where the use of centrally acting anti-tussives is undesirable.

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