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The antitussive actions of the drug Ru 20201 given as an aerosol to cats

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The effect of the drug Ru 20201 (1,2,3,4,4a,9b-hexahydro-8,9b-dimethyl-4-[3-(4-methyl-piperazin-1-yl)propionamido]dibenzofuran-3-one upon mechanically-evoked cough from the laryngopharyngeal and tracheobronchial areas in nine unanaesthetized cats has been examined. Inhalation of 2 ml of an aerosol of a 10% solution in water suppressed coughing for 30 min. The effect was greatest on the number of cough efforts. The expiratory component of cough was suppressed more than was the inspiratory one. The effect was greater on cough from the laryngopharyngeal than from the tracheobronchial area.

There have recently appeared descriptions of attempts to apply by aerosol inhalation, antitussive drugs presumably with a peripheral action. Most studies have been with drugs that are established local anaesthetics; they have either been with anaesthetized animals or with patients, and in each case the interpretation of results in terms of mechanisms of cough is limited. Dain, Boushey & Gold (1975) eliminated a mechanically evoked cough from the trachea and carina of anaesthetized dogs and rabbits by use of an aerosol of 5% bupivacaine hydrochloride, a locally-acting anaesthetic. Cross, Guz & others (1976) obtained a similar effect with bupivacaine in anaesthetized dogs and in unaesthetized man. Kandus & Utrata (1976) apparently succeeded in depressing cough in patients with chronic non-specific bronchopulmonary diseases, using Thiameton Spofa by inhalation.

We have used a preparation originally developed to study the mechanisms of coughing in unanaesthetized cats (Korpas, Bilcik & Kohut, 1964), applying it to an antitussive drug given by aerosol. This approach has the advantage that it combines for the first time an analytical method to investigate coughing in the absence of general anaesthesia, with an aerosol-administered drug developed for its antitussive rather than local anaesthetic properties. The drug is Ru 20201 (Lot 6, Roussel Ltd; chemical formula 1,2,3,4,4a,9b-hexahydro-8-9b-dimethyl-4-[3-(4-methylpiperazin-1-yl)propionamido]dibenzofuran-3-one dihydrochloride). Its general pharmacology in anaesthetized animals has been described (Matharu, Rowlands & others, 1977; James & Pickering, 1978; Pickering & James, 1978). Since it might be of value as an antitussive aerosol in patients, its action on mechanically evoked cough in conscious cats seems of interest.

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MATERIALS AND METHODS

Nine healthy cats of either sex, mean weight 2 kg, had a chronic T-shaped tracheal cannula surgically inserted under general anaesthesia before the tests Korpas & others, 1964). Subsequent tests were made after the cats had recovered from the anaesthesia and surgery. The side-arm of the cannula was connected to an electromanometer, and the resultant pressure records gave a qualitative index of cough. The cannula allowed insertion of a nylon fibre into the airways to stimulate the airway mucous membrane mechanically. Coughing was evoked by stimulation of the laryngopharngeal and the tracheobronchial areas. It was evaluated by the number of cough efforts, their frequencies and the intensities of the maximum efforts during the expiratory and inspiratory phases; in addition we calculated the means of the strengths of the expiratory and inspiratory efforts in each attack of coughing; this last assessment has been evaluated previously (Korpas & Tomori, 1975). The nylon fibre was always inserted to the same depth to ensure stimulation of the same part of the mucous membrane. It was gently pulled and pushed during a period of about 5 s. Cough was induced and recorded before administration of the antitussive drug (control) and at 1, 5, 15, 30 and 60 min after administration.

The drug was administered through a glass nebulizer taken from a Pulfrich's flame photometer, using a jet No. 4.04 at an air pressure of 0·6 Atm. The size of particles ranged from 10–2 μm, which should be deposited throughout the airways (Findeisen, 1935; Stuart, 1973; Widdicombe, 1977).

The aerosol would be both inhaled caudally (into the lungs) and exhaled cranially (into the larynx). The mouths of the animals were held open. Initially, the aerosol of Ru 20201 (in a 10% solution in water) was administered to animals through the intratracheal cannula for a period of 1 min. The total amount of the solution was 0·4 ml, equivalent to 0·04 g of the drug. The proportion of this which was retained in the airways is not known. Since this dose seemed ineffective, we extended the period of administration to 3 min; during that time 2 ml of solution (0·2 g of drug) left the nebulizer and, as indicated below, had an antitussive effect.

After the first investigations (series 1), the same animals were studied after a further 2–3 days (series 2). The Wilcoxon & Wilcox (1964) rank test was used for statistical evaluation.

RESULTS

At 1–30 min after inhalation of the aerosol, the cough reflex was depressed, and by 60 min the intensity of cough had reverted to control values.

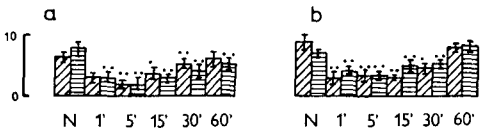

FIG. 1. Number of cough efforts (ordinate) from laryngopharyngeal (a) and tracheobronchial (b) areas. Comparison of changes in normal controls (N) with responses at intervals (min) after administration of Ru 20201. Values are mean and standard errors. ● = $P < 0{\cdot}05$, ●● = $P < 0{\cdot}01$. Diagonally hatched columns are results from initial experiments. Cross hatched columns are results from repeat experiments 2–3 days later.

Fig. 1 shows that the number of cough efforts was decreased by 60–70% for stimulation at both the laryngopharyngeal and the tracheobronchial sites.

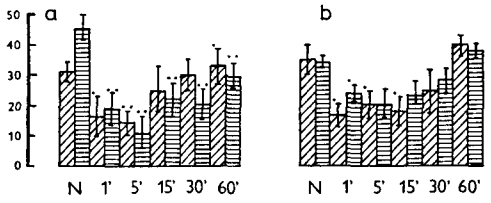

FIG. 2. Frequency of coughs (min^{-1}) (ordinate) before and after administration of Ru 20201. Results expressed as in Fig. 1.

Fig 2 shows that the change in frequency was significantly greater for the laryngopharyngeal cough (mean decrease of over 60%) than for the tracheobronchial cough (40%). Maximal intensity of the expiratory efforts of cough was also depressed more for the laryngopharyngeal site (over 60% decrease) than for the tracheobronchial one (about 40%) (Fig. 3). The inspiratory efforts were less depressed (20–30% decrease). The mean strength of the

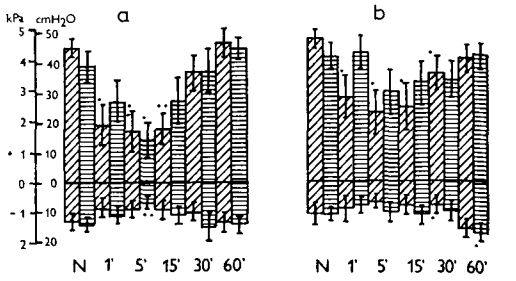

FIG. 3. Maximum intensity of coughs (ordinate) in expiratory (+) and inspiratory (−) phases. Results expressed as in Fig. 1.

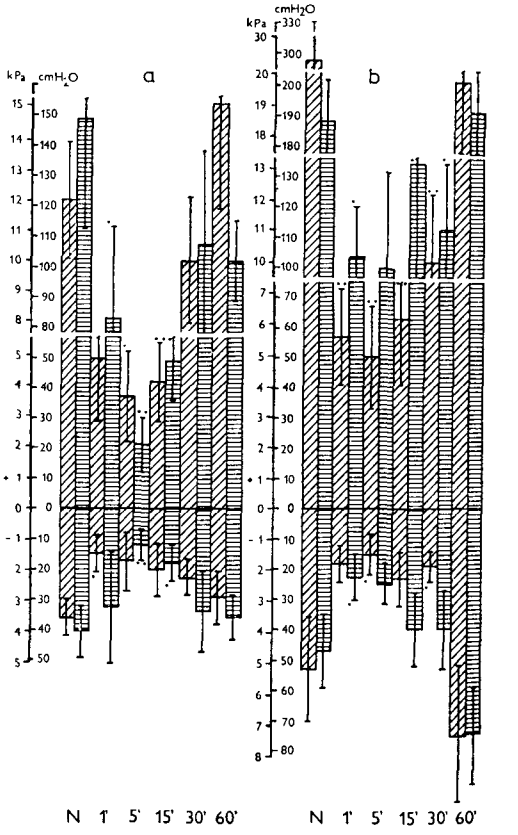

FIG. 4. Mean intensity of coughs (ordinate) in expiratory (+) and inspiratory (−) phases. Results expressed as in Fig. 1.

expiratory efforts was decreased by about 80% for the laryngopharyngeal site and by about 60% for the tracheobronchial site (Fig 4). The mean strength of the inspiratory efforts was decreased by about 50%.

In most instances, repetition of the experiments after 2–3 days (series 2) gave similar results to the initial tests (series 1) (Figs 1–4).

DISCUSSION

The method we have used, previously applied to study the physiology of cough mechanisms, has proved to be suitable for study of aerosol administered antitussive drugs. The method allows coughing to be induced from different sites and to be analysed into different components, which might be of interest in comparing the actions of different antitussive drugs. It has the advantage over similar methods in anaesthetized animals in that there is no general anaesthetic to interact with the drug, and over studies in unanaesthetized man in that ethical considerations limit the methods of inducing coughing in man. No clinical description of the use of Ru 20201 as a aerosol antitussive has been published.

Ru 20201 seems to depress the cough reflex within 1 min, with a maximum between 1 and 15 min, and is still partially active after 30 min. We assume that the drug acts by a local analgesic or anaesthetic effect, but other possibilities have not been eliminated, e.g. an action on the amount or viscosity of the mucus, on humidification of the respiratory tract, or by relaxation of the smooth muscle of the bronchi (Bickerman, 1960).

The antitussive effect of Ru 20201, as given in our experiments by aerosol, is somewhat weaker than that of 10 mg kg^{-1} of codeine given intraperitoneally to conscious cats in similar conditions (Strapkova, Korpas & others, 1975).

Analysing the effect on different types of cough, we noticed that Ru 20201 was more active against cough induced from the laryngopharyngeal compared with the tracheobronchial area. In the controls, the characteristics of the coughs were equally intense from both sites. This result could be explained by a greater deposition of the aerosol on the smaller laryngopharyngeal surface. Alternatively, the difference could be due to the different nerve supply to the two stimulated areas (Korpas & Tomori, 1975). The expiratory values of both types of cough had a significantly larger decrease in response to the drug than did the inspiratory values. The strongest effect of the drug was on the number of cough efforts, which value probably depends on the state of the cough receptors, while the strength of cough may be more determined by the state of the 'cough centre' in the brain stem (Korpas & Tomori, 1975).

Although the doses of drug needed to inhibit the cough were large, the mechanical stimulus to coughing was intense. Even in anaesthetized animals, where the general anaesthetic might have a cough depressant effect, the dose of a parenterally administered antitussive drug (codeine) may be 10–20 times larger on a body weight basis than that normally used in man (May & Widdicombe, 1954).

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