

Short communication

Bronchopulmonary effects of elliptinium in anesthetized dogs

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Summary. The bronchoconstrictor effect of elliptinium already demonstrated in the guinea-pig is shown in the dog. It is less intense and its onset is prompter. Successive administration of identical doses of elliptinium attenuates the bronchospasm induced, suggesting tachyphylaxis. The previously described indirect bronchoconstrictor effect involving endogenous mediators seems also to be active in these circumstances.

Introduction

Previous work [1] demonstrated the bronchoconstrictor activity in the guinea-pig of the new antitumor agent 9-hydroxy-2-methyl-ellipticinium acetate (elliptinium) [3, 5,]. This activity is more progressive than that of histamine, and is tachyphylactic. Furthermore, the constrictor effect, which is inhibited in vivo by prior administration of antihistamines, is not observed in the isolated trachea. Evidently then, this effect has an indirect mechanism involving bronchial H_1 histamine receptors to a large extent. The bronchoconstrictor effect of elliptinium has been observed in man: Rouesse et al. [6] reported the onset of dyspnea with bronchospasm during perfusion.

This work aimed to establish whether this effect occurred in the dog, by studying the response to different doses administered as a bolus injection and looking for tachyphylaxis.

Materials and methods

Animals. Eleven mongrel dogs of both sexes, weighing 18 ± 2.4 kg, were fasted overnight before the study. They were housed in individual cages in a large colony room.

Procedure. All the dogs were anesthetized with chloralose (80 mg/kg, IV) after a prior injection of sodium pentobarbital (6 mg/kg IV). They were then tracheotomized and ventilated artificially with room air. A catheter was led off from the tracheal cannula to a Statham P23 V transducer. Bronchopulmonary pressure, obtained according to the method of Konzett and Rössler [4], was recorded on a Beckman type RP polygraph. The bronchomotor effect of elliptinium was quantified in terms of amplitude of trace displacement. An increase in amplitude indicated a bronchoconstriction.

Drug treatment. Two series of experiments were carried out: in the first, six dogs each received a dose of 3 mg/kg IV every 50 min, four doses being given in all; and in the second five dogs were each given a single dose of 5 mg/kg IV. The elliptinium was always dissolved in distilled water. The solution was injected over 30 s, with a constant volume of 0.5 mg/kg. Doses are given in terms of the salt.

Statistical analysis. Results were expressed as means \pm SEM, and statistical analysis of the data was carried out with a two-way analysis of variance followed by Student's *t*-test.

Results

Elliptinium induced dose-dependent bronchoconstriction (Fig. 1). An increase in trace amplitude ($+3.1 \pm 0.47$ mm) was obtained after the first dose of 3 mg/kg, though the variation was not significant. For the dose of 5 mg/kg, the effect was more marked ($+8.2 \pm 3.3$ mm) and the difference was significant. In both cases the maximal effect occurred within the 1st min after injection. Thereafter, values were not statistically different from those at the start of the experiment. After the second and third doses of 3 mg/kg, the bronchoconstriction was significantly attenuated (Fig. 2). That

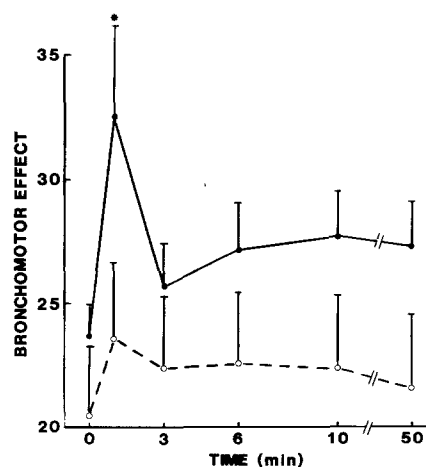


Fig. 1. Bronchoconstrictor of elliptinium, 3 mg/kg (○---○) and 5 mg/kg (●—●). The bronchomotor effect was quantified in terms of amplitude (mm) of trace displacement. Bars indicate SEM. * $P < 0.05$ versus predrug values

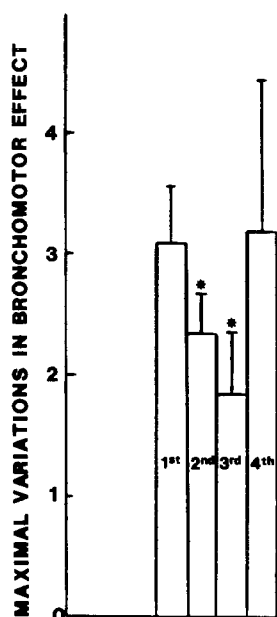


Fig. 2. Reproducibility of bronchoconstrictor activity of elliptinium after four successive injections of 3 mg/kg. The variations in the bronchomotor effect were quantified in terms of variation of amplitude (mm) of trace displacement. Bars indicate SEM. * $P < 0.05$ versus first injection effect

recorded after the fourth dose of 3 mg/kg was not statistically different from that after the first dose, though the range was very wide at this stage of the experiment.

Discussion

In the dog, which as a species is less sensitive than the guinea-pig with regard to bronchopulmonary response, elliptinium induces dose-dependent bronchoconstriction. Administration of three successive doses of elliptinium (3 mg/kg)

produced marked attenuation of the bronchoconstrictor effect initially obtained. This strongly suggests tachyphylaxis. The response after the fourth injection failed to confirm this, though the wide range of values obtained makes interpretation of this observation difficult. These results are consistent with those obtained in the guinea-pig [1], though the effect is less intense and its onset prompter. The apparent tachyphylaxis supports an indirect mechanism via endogenous mediators. Histamine release induced by elliptinium both in vivo in the guinea-pig and in vitro in human tissue [2] seems likely to be involved in these bronchial effects.

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