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Effects of H1 antihistamines on canine nasal vascular and airway resistances

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SUMMARY

The effects of three commonly used H1 antihistamines on the nasal vascular and airway resistances were studied in the dog. Promethazine hydrochloride decreased nasal vascular resistance but increased nasal airway resistance in a dose-dependent manner. Diphenylpyraline hydrochloride in low doses increased nasal vascular resistance without affecting much nasal airway resistance while in high doses decreased nasal vascular resistance but increased nasal airway resistance. Chlorpheniramine maleate in low doses increased nasal vascular resistance but decreased nasal airway resistance while in high doses decreased nasal vascular resistance without affecting much nasal airway resistance. It was concluded that different H1 antihistamines might exert vasoconstrictor or vasodilatatory action on both the resistance and capacitance vessels of the nasal vascular bed depending on the type and the dose of the drug used.

INTRODUCTION

In patients with allergic rhinitis, inhaled allergen causes an immediate hypersensitivity of the nasal mucosa resulting in sneezing, hypersecretion and congestion. Histamine has been believed to be the principal mediator responsible for the symptoms as mast cells of the nasal mucosa show signs of degranulation (Mygind, 1978). Therefore, antihistamines are commonly used in the symptomatic treatment of nasal allergy and many attempts have been made to study the effectiveness of these drugs on the nasal airway response to histamine (Bentley and Jackson, 1970; Matson et al., 1978). However, the direct action of these drugs on the nasal vasculature is still unclear.

We have developed a technique to measure directly and simultaneously nasal vascular and airway resistances in the dog. In the present study, we have applied such a technique to study the effects of three commonly used H1 antihistamines on the nasal vascular bed.

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METHODS

The experiments were carried out with mongrels, weighing between 15 to 20 kg, of either sex, anaesthetized with intravenous injection of sodium pentobarbitone (25 mg/kg). Tracheotomy was performed and the tracheal cannula was connected to a Fleisch pneumotachograph to give airflow and tidal volume by electric integration. Both femoral arteries were cannulated. One catheter was used for measurement of the systemic arterial blood pressure and the other catheter for supplying blood to the nasal perfusion circuit. Heparin (1000 units/hr) and supplementary doses of anaesthetic were given via a femoral venous catheter.

Vascular perfusion of the nasal mucosa was carried out separately on both sides as previously described (Lung and Wang, 1984). The terminal branch of the internal maxillary artery is the main arterial supply to the septum, turbinates and lateral walls of the nasal cavity (Dawes and Prichard, 1953). An infraorbital dissection was made along the zygomatic region to expose the internal maxillary artery and its infraorbital and terminal branches. The terminal branch of the internal maxillary artery was perfused at a constant flow rate with blood from the femoral artery via the infraorbital catheter. Perfusion rate was adjusted to give a perfusion pressure close to the systemic arterial blood pressure. Changes in the nasal vascular resistance were reflected by changes in the vascular perfusion pressure.

Nasal airway resistance was assessed separately on both sides as previously described (Lung and Wang, 1984). A stream of humidified air was allowed to pass through each side of the nose at a constant flow rate and the nasal airway pressure was monitored. Changes in the nasal airway resistance were reflected by changes in nasal airway pressure.

All flow and pressure variables were recorded on a dynograph (Beckman). Drugs were injected directly into the nasal vascular bed in 0.1 ml saline via the perfusion circuit. These include promethazine hydrochloride (Phenergan®; May and Baker), diphenylpyraline hydrochloride (Histryl®; Smith, Kline and French) and Chlorpheniramine maleate (Chlor-trimeton; Schering). Doses were expressed as weight of the salt. Drugs were injected at intervals on alternate sides of the nose.

RESULTS

Table 1 summarizes the nasal vascular and airway responses to the H1 antihistamines. Figure 1 shows experimental records illustrating the results.

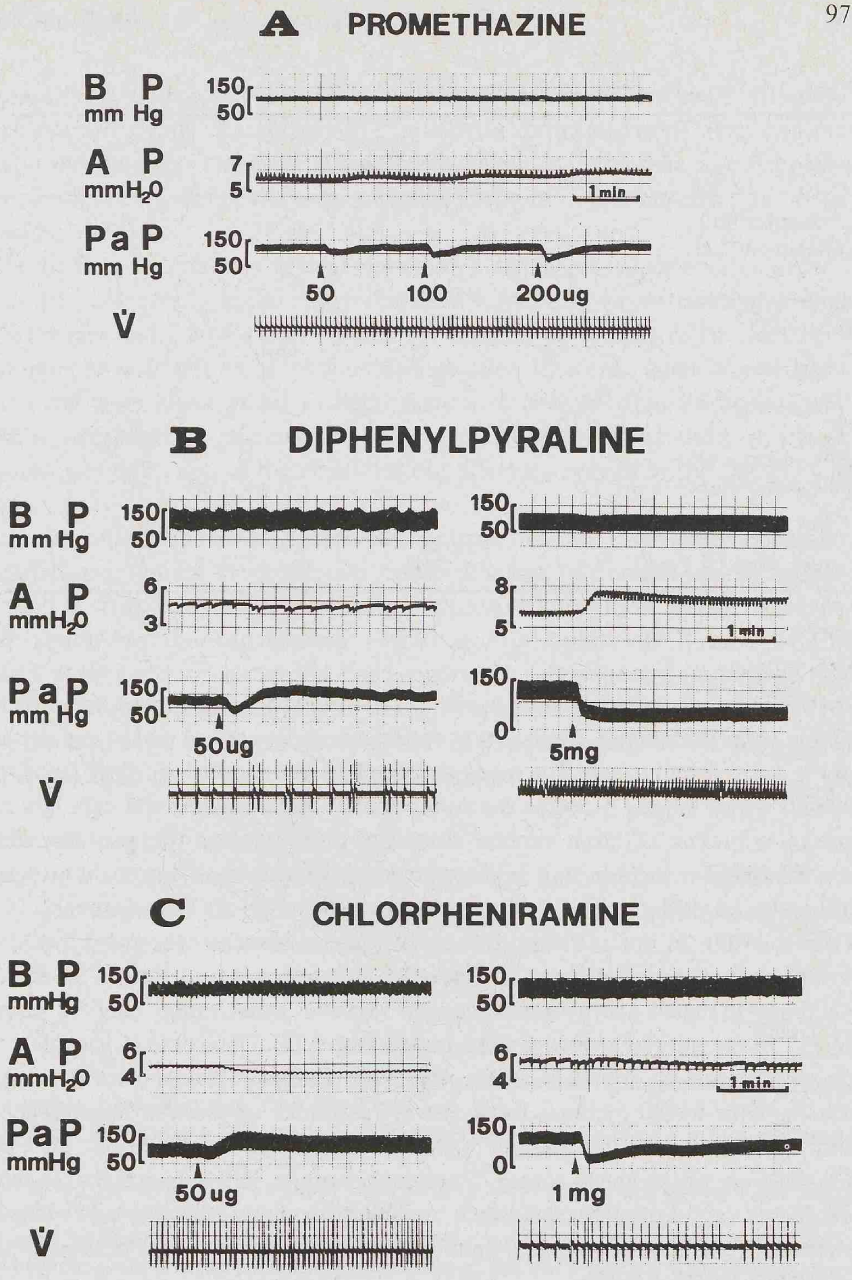

Figure 1. Effects on nasal arterial perfusion pressure and airway pressure after intra-arterial injection of A, promethazine hydrochloride (50 µg, 100 µg and 200 µg in 0.1 ml saline), B, diphenylpyraline hydrochloride (50 µg and 5mg in 0.1 ml saline) and C, chlorpheniramine maleate (50 µg and 1mg in 0.1 ml saline), injected at arrows. Traces from above downwards in each record: systemic arterial blood pressure (BP), nasal airway pressure (AP), nasal arterial perfusion pressure (PaP) and tracheal airflow ($\dot{V}$).

Table 1. Summary of nasal responses to H1 Antihistamines.

	vascular resistance	airway resistance
promethazine (phenergan®)	↓	↑
diphenylpyraline (histryl®)		
low dose (< 1 mg)	↑	(↓)
high dose (> 1 mg)	↓	↑
chlorpheniramine (chlor-trimeton)		
low dose (< 1 mg)	↑	↓
high dose (> 1 mg)	↓	(↓)

DISCUSSION

As the nasal cavity is basically made up of a bony structure lined by a layer of highly vascular mucosa, nasal airway resistance is dependent on the capacitance of the nasal vascular bed. The nasal vascular bed includes precapillary resistance vessels which supply blood to the subepithelial and periglandular capillary networks, a plexus of large venous sinusoids draining into the venules which are relatively muscular, and numerous arteriovenous anastomoses which may allow the blood to bypass the capillary-sinusoid networks (Temesrekasi, 1969; Cauna, 1982). In our constant-flow perfusion experiments, the same total flow would be distributed through the vascular channels per unit time. Therefore, a decrease in nasal airway resistance or vascular capacitance may be caused by (1) an opening of arteriovenous anastomoses; (2) a decrease in vascular outflow resistance by dilatation of the muscular venules. The opposite changes in mechanisms would increase nasal airway resistance or vascular capacitance.

Promethazine hydrochloride decreased nasal vascular resistance but increased nasal airway resistance in a dose-dependent manner. This suggests that the drug decreases vascular inflow resistance by dilatation of the arterioles and increases vascular capacitance by closing up of arteriovenous anastomoses or constriction of the muscular venules.

Diphenylpyraline hydrochloride, in doses less than 1 mg, increased nasal vascular resistance but decreased only slightly nasal airway resistance. This suggests that the drug in such doses exerts a constrictor effect on the arterioles and its effect on the capacitance vessels is very minor. When doses higher than 1 mg were given, nasal vascular resistance was decreased while nasal airway resistance was

increased. This suggests that the drug in high doses has a reverse effect on the resistance vessels, changing from a constrictor action into a dilatatory one and also the capacitance vessels are affected resulting in an increase in vascular capacitance via closing up of the arteriovenous anastomoses or constriction of the muscular venules.

Chlorpheniramine maleate, in doses less than 1 mg, increased nasal vascular resistance but decreased nasal airway resistance suggesting a constrictor action on the arterioles and a decrease in vascular capacitance by opening of arteriovenous anastomoses or dilatation of the muscular venules. However, when doses higher than 1 mg were given, nasal vascular resistance decreased significantly while nasal airway resistance decreased only slightly. This suggests that the drug in high doses causes dilatation of the arterioles but affecting very little the capacitance vessels.

Many clinically used H1 antihistamines has been found to exert dose-dependent constriction action on the resistance vessels of several different vascular beds in vivo and in vitro (Altura and Zweifach, 1965; Altura and Altura, 1974). However, their action on the capacitance vessels is still unknown. Results of the present study indicate that unlike their general action on the systemic blood vessels H1 antihistamines may cause vasoconstrictor or vasodilatatory action on both the resistance and capacitance vessels of the nasal vascular bed depending on the type and the dose of the drug concerned.

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