Non-Specific Airway Hyperreactivity in Horses and the Influence of Corticosteroids

H.-J. Klein and *E. Deegen*

Klinik für Pferde, Tierärztliche Hochschule Hannover

Introduction

The sensitivity of the airways to react with a bronchospasm, known as airway reactivity, can be determined in horses in a way similar to that used in humans. As early as 1948, *Obel* and *Schmiterlöw* assessed changes in the maximal intrathoracic differences in pressure after intravenous histamine administration in horses. For the purpose of determining intrathoracic pressure, the authors created an artificial pneumothorax and connected this to a pressure-measuring instrument. *Obel* and *Schmiterlöw* detected increased histamine sensitivity in horses suffering from heaves as compared to healthy horses.

In a manner similar to that used by *Obel* and *Schmiterlöw, Derksen* et *al.* (1982) administered histamine to healthy, sedated ponies intravenously. The histamine effect was assessed by means of a complete lung function test.

Eyre and *Mirbahar* (1983/1984) had healthy horses and those suffering from COPD inhale the same dose of histamine. Those horses suffering from COPD revealed a significant hyperreactivity to inhaled histamine.

Klein (1984) determined the presence of airway reactivity in horses by causing them to inhale solutions with increasing histamine content and in each case carried out subsequent lung function tests. This investigation revealed that one quarter of horses suffering from COPD to a slight degree and all of those suffering from severe COPD showed a non-specific airway hyperreactivity. Mainly fully-grown warm-blooded horses were chosen for the tests which, during the test, were under the influence of no other drugs.

Derksen et *al.* (1985), too, had ponies inhale solutions with increasing histamine content for the purpose of determining non-specific airway hyperreactivity. Ponies with a history of heaves showed, after being kept on pasture, the same reactivity as ponies without a history of airway obstruction. After being housed in a barn, the reactivity of ponies with a history of heaves was significantly higher but the reactivity of the control ponies remained unchanged.

As research work has hitherto shown, horses suffering from COPD and heaves respectively, often show a non-specific airway hyperreactivity. Non-specific airway hyperreactivity in humans has been demonstrated in connection with numerous respiratory diseases.

Undoubtedly, non-specific hyperreactivity is of great significance both for the development as well as for the continuation of lung diseases. It would thus be important to be able to lower the non-specific hyperreactivity by drugs. In this context, corticosteroids in particular were tested for their influence on airway hyperreactivity in humans. These tests yielded completely different results for different investigators.

Easton (1980) was unable to detect any improvement in non-specific airway hyperreactivity in asthmatics after the patients had inhaled beclomethasone for 4 weeks. In contrast to this, *Juniper* et *al.* (1982) found that 14 out of 15 asthmatics had a significantly increased $PC_{20}FEV_1$ after 12 to 30 months of inhaling beclomethasone daily.

Other authors investigated the influence of prednisone on non-specific airway hyperreactivity. This corticosteroid was administered in tablet form. The daily dose was between 30 and 128 mg and the time of administration varied between 2 days and 2 weeks.

Wolfe et *al.* (1979) found no changes in the reactivity in 5 asthmatics after administration of prednisone. *Spector* and *Farr* (1975) found the same result, although in their case a few patients showed some improvement in their reactivity. Asthmatics tested by *Arkins* and *co-workers* (1968) even revealed a significant increase in their reactivity. COPD patients reacted, however, with an insignificant decrease of airway reactivity.

In the above-mentioned investigations, it was not always possible to standardize all factors which influence airway reactivity. The tests carried out by *Israel* and *co-workers* (1984) were methodically more exact. These authors investigated the influence of two doses of oral methyl prednisolone on non-specific airway hyperreactivity in asthmatics. The test subjects swallowed 2 tablets each on the evening before and on the morning of the test. The total doses were 32 mg and 128 mg of methyl prednisolone respectively. Methyl prednisolone decreased airway reactivity significantly. The higher dose showed no increase in efficacy when compared with the lower dose.

The positive results of *Israel* and *co-workers* (1984) encouraged initiation of this project to examine the influence of corticosteroids in non-specific airway hyperreactivity in horses.

Material and Methods

After a clinical and tracheobronchoscopic examination and an analysis of the arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), 8 horses were found to be suffering from severe COPD.

Clinical signs included respiratory distress at rest, pathologic sounds upon lung auscultation and a caudoventral dislocation of the lung border. Tracheobronchoscopy revealed medium to large amounts of bronchial mucus. PaO_2 was reduced in all cases (< 95 mm Hg).

A histamine inhalation provocation test (HIPT) was carried out on these 8 horses according to the method described by *Klein* (1984). For this purpose, the horses stood in a stock, were fastened by a strap and tied up to both sides. An esophageal balloon was inserted into the midthoracic portion of the esophagus and the horses were fitted with a face mask. The esophageal balloon was connected to a pressure transducer and a flow transducer was fitted into the opening of the face mask. A measuring and recording instrument (Hellige, Freiburg) recorded esophageal pressure,

Fig. 1: A horse fitted with a face mask and inhaling a test solution during the histamine inhalation provocation test (HIPT).

a pneumotachogram and a spirogram simultaneously. In addition, an X-Y recorder registered pressure-volume loops from which dynamic compliance (Cdyn) was calculated.
The flow transducer in the opening of the face mask was then exchanged for a nebulizer adapter. The nebulizer – a "Respineb Nebulizer" (Aerosol Products, London) – was filled with approximately 3 ml of the test solution, connected to compressed air and connected to the adapter (Fig. 1). Test solution I was the solvent for the histamine solutions to follow, and was in fact a phosphate buffered solution containing sodium chloride pH 7.4 as described in the European Pharmacopeia.
The horses inhaled each test solution for exactly 2 minutes. The "Respineb Nebulizer" nebulised 0.16 ± 0.01 ml/min. Approximately 60 seconds after the inhalation of each test solution, lung function was re-measured. Test solution II contained 0.125 mg of histamine dihydrochloride per ml. The histamine concentration of the following test solutions was doubled each time (Fig 2). The test was continued until the respiratory distress of the horses increased significantly and Cdyn had fallen to approximately half its initial value.
Evaluation of the HIPT was carried out using a linear regression between the histamine concentration and the Cdyn value (Fig. 3). The histamine concentration which, according to the lines of regression, would have effected a 35 % reduction of the Cdyn value was calculated, and this histamine concentration was called PC_{35}Cdyn (PC = provocating concentration). The smaller PC_{35}Cdyn, the greater is the non-specific airway hyperreactivity.
The HIPT always started between 1 and 2 p.m. Subsequent to the first trial, each horse was given a total of 3 intramuscular injections of 0.4 mg each of prednisolone acetate per kg of body weight. We used Hostacortin®-H (Hoechst, Frankfurt). The first injection was given immediately after the first trial, and the second and third injection were given in the morning 24 and 48 hours after the first trial respectively. Between 1 and 2 p.m. of the second day after the

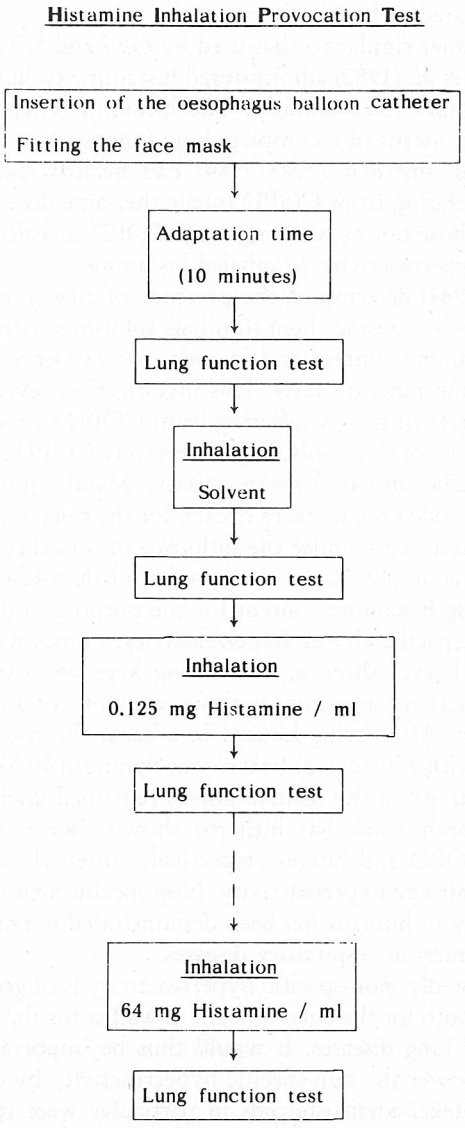

Fig. 2: The experimental design of the HIPT.

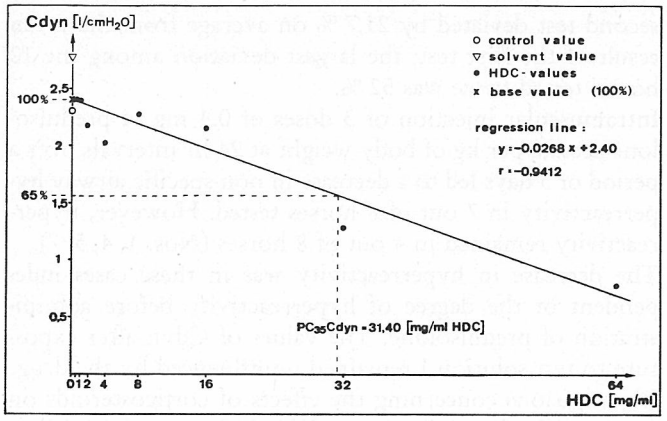

Fig. 3: The evaluation of the HIPT carried out with the use of a linear regression between histamine concentration and dynamic compliance (Cdyn). This is an example for a horse without respiratory signs.

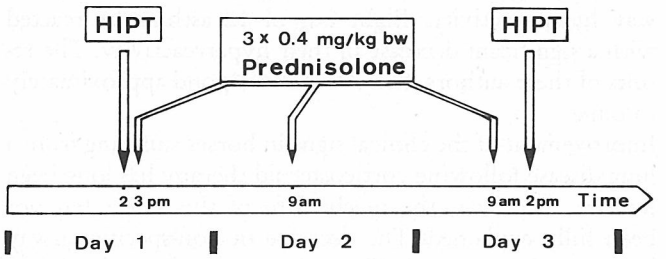

Fig. 4: The test procedure of this investigation.

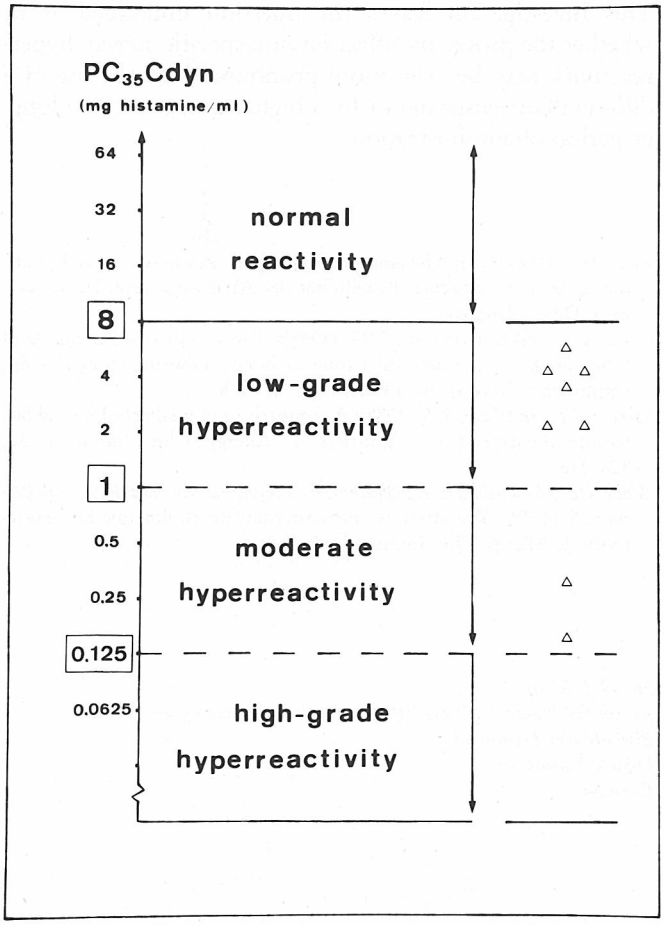

Fig. 5: The classification of the reactivity grades by *Klein* (1984) and the distribution of the PC_{35}Cdyn values of the 8 horses tested in this study before the administration of prednisolone.

first trial, the non-specific airway reactivity was again calculated by means of the HIPT as described above (Fig 4).

Results

Before administration of corticosteroids PC_{35}Cdyn values of the 8 test horses were between 0.15 and 5.85 mg of histamine dihydrochloride per ml of solution. In accordance with the classification of reactivity grades by *Klein* (1984), 6 horses showed a low-grade and 2 horses a moderate non-specific airway hyperreactivity (Fig. 5).

After three doses of corticosteroid, the values of Cdyn taken before exposure to test solution I did not change significantly. In one horse Cdyn improved and in one horse it worsened. The mean value remained constant at 0.56 l/cm H_2O.

The influence of the corticosteroid treatment became, however, quite significant after histamine exposure. With respect to the effect on airway hyperreactivity, the 8 horses tested may be divided into three groups (Fig 6).

PC_{35}Cdyn remained almost the same in one horse (No. 5). The second group is formed of 3 horses (Nos. 4, 7, 6) which showed a significant increase in the PC_{35}Cdyn of 65, 93, and 114 % respectively. The third group consists of 4 horses (Nos. 8, 2, 3, 1) which showed a drastic increase in the PC_{35}Cdyn of 460, 760, 1290, and 1870 % respectively.

After the three-day administration of prednisolone, airway hypersensitivity had thus decreased significantly in 7 out of 8 horses tested.

The varying decrease in non-specific airway hyperreactivity was independent of the PC_{35}Cdyn value of the first HIPT, i. e., independent of non-specific airway hyperreactivity before the administration of prednisolone.

Discussion

A prerequisite of the comparison of two test results is the reproducibility of the test. In an earlier investigation, the

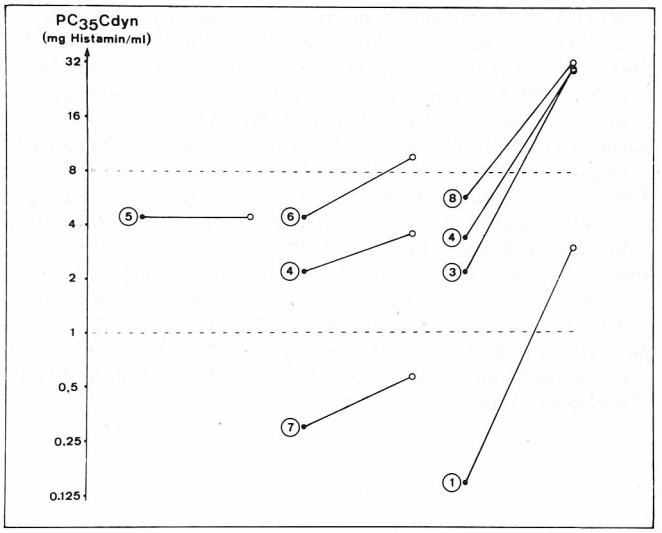

Fig. 6: PC_{35}Cdyn values before (closed circles) and after the three-day administration of prednisolone (open circles). – An increase in PC_{35}Cdyn implies a decrease in non-specific airway hyperreactivity.