Introduction
Respiratory problems are frequently implicated in horses as a cause of poor sportive performances. The most frequently occurring lower respiratory tract disorders are heaves, inflammatory airway disease and exercise-induced pulmonary haemorrhage (EIPH) [1]. Classically, their treatment included systemic administration of drugs, however, aerosol therapy is now known to be a more specific way to treat respiratory disorders with a better efficacy/toxicity ratio. Furthermore, the recent development of easy-to-use devices for horses has boosted the interest for such a therapy. This article describes the equipment and drugs currently recommended for aerosol therapy in horses.

Definition
Aerosol therapy or inhalation is a method of drug administration directly to the respiratory system. Because the drugs are deposited locally in the airways, aerosol therapy allows lower dosage, has a rapid action and minimises the incidence of side effects and systemic toxicity. The aerosol contains microdroplets of medication. It may be produced by nebuliser, metered-dose inhaler and dry powder inhaler relative to the physical aspect of the medication (i.e. liquid, gas or solid, respectively).

Particle Deposition in the Airways
The deposition of an aerosol is determined primarily by its size, deposition site becoming deeper as the particle size is reduced. The filtration function of the nasal chambers ensures that particles of 5-10 µm are entrapped in the upper airways, whereas 90% of particles less than 0.5 µm are exhaled [2]. Most of the aerosol is deposited in the alveoli if particle size is less than 2 µm [3].

Two main physical mechanisms cause the deposition of aerosols in the airways: inertial impaction and sedimentation [4]. Inertial impaction occurs mainly with larger particles or when the air stream is moving rapidly and changing direction. It enhances deposition in the central airways. Gravitational sedimentation allows deposition of particles which are able to penetrate to the more peripheral parts of the respiratory tract. Other mechanisms of deposition due to diffusion (Brownian movements), electric forces and interception can also occur, but their roles are probably of little relevance for therapeutic aerosols. Aerosolized particle diameter and hence particle deposition is also influenced by properties of the aerosol itself (viscosity, density, surface tension of the nebulised solution, hygroscopic growth) [5,6], and the patient (anatomy, pathophysiology, breathing pattern) [7,8].

Required Qualities of Aerosolized Therapeutic Drugs
Not all drugs used for systemic treatment can be used for inhalation. Indeed, many physical and chemical factors influence the action of an aerosol, e.g., viscosity and tonicity. Generally, aerosolized solutions should be isotonic. Mann et al., [9] showed that nebulised hypotonic ipratropium bromide caused bronchoconstriction and that reformulation as an isotonic solution may prevent this risk. In addition, certain components of aerosolized solutions may cause bronchoconstriction, e.g., benzalkonium, EDTA, chlorbutol, edetic acid and metabisulphite should not be included in aerosols [10,11].

Types of Inhalation Devices
Therapeutic aerosols are commonly produced by atomisation of liquids within jet (or pneumatic) nebulisers or by vibration of a standing pool of liquid (ultrasonic nebulisation). Aerosols may also be administered by use of metered-dose inhalers (MDIs) and dry powder inhalers (DPIs).

While all of these systems produce respirable particles, there is great variation in efficiency of nebuliser-compressor combinations in drug delivery to the lungs [12]. Moreover, each delivery system and drug combination has unique deposition characteristics which should be studied individually. It is also noteworthy that material may be contaminated with bacteria or
fungi so that disinfection of equipment (e.g., cupules, connector and face mask) is of great importance.

Jet Nebulisers - The jet nebuliser uses a powerful dry air compressor (minimum 6 bars) (Fig. 1 and Fig. 2) to generate high air flows across the liquid medication to produce small diameter aerosol particles. By altering gas flow rate, size of the aerosol particles and hence their pulmonary distribution, can be varied. The major disadvantage of this type of nebuliser is the noise produced by the compressor. It should be noted that generation of an aerosol with a diameter less than 5 µm, requires a minimal air flow of 6 to 8 l/min at the input of the jet nebuliser [13,14]. Jet nebulisers available commercially in human medicine are cheap and easy to use. Unfortunately, their low air flow rate and lack of robustness normally make them unsuitable for horses. One type however, has been adapted for the equine use and its efficacy to deposit aerosols in the lung has been demonstrated in the horse [15].

Ultrasonic Nebulisers - In ultrasonic nebulisers, the aerosol is produced by the vibration of a piezo-electric crystal at a high frequency (minimum 1.6 MHz) (Fig. 3 and Fig. 4). These devices can produce highly concentrated aerosols [16] and are relatively silent. However, their use is limited by their price and fragility. Additionally, the diameter of generated particles is greater than those obtained using jet nebulisers at high air flow rates [15,17]. Effective drug administration has been demonstrated with this kind of nebuliser in horses suffering from heaves [18,19].

Metered-dose Inhalers (MDI) - Agents for MDI administration are presented in a compact aerosol container allowing patients to deliver an accurate dose of the drug through a metering valve during inspiration [20]. Adaptation of MDI to use in horses led to the development of several systems, e.g., the Equine Aeromask™ (Fig. 5) [21-23] and the Equine Haler™ (Fig. 6) [24].
The MDI is actuated into the spacer with a one-way inspiratory valve and the drug is inhaled through the spacer to facilitate administration of the aerosol and to increase small diameter particles inhalation. These systems are inefficient if leakages appear at the level of valves or at the level of the connection between the devise and the face of the horse.

Another system, which avoids the use of a face mask and valves, consists of a spacer, a triggering device and a MDI canister (Fig. 7) [23,25]. A flag attached to the device indicates inhalation and exhalation, which allows the user to improve synchronisation between the manual drug delivery and the horse’s inspiration.

Dry powder inhalers (DPI) - The DPIs are breath-actuated devices, designed to generate the aerosol when the inspiratory airflow of the patient crosses the device containing the drug. The airflow must be high enough to deaggregate the dry powder drug so that the patient inspires the medication without requiring synchronization between manual delivery of the drug and a deep inspiration [8]. There are essentially 2 types of DPI: the first uses agents filled into a gelatin capsule, and the second has a reservoir that can be used on a multiple-dose basis [26]. The absence of CFC propellants and their minimal external loss of aerosol make DPIs an environmentally friendly option. Some DPIs require inspiratory flow rates of 60 l/min to deaggregate the powder effectively; although this sometimes presents difficulties for asthmatic human patients, it is easily achieved in either healthy or heaves-affected horses. The adaptation of the DPI for use in the horse necessitates an airtight face mask (Fig. 8) [27].

Therapeutic Approach to Respiratory Disorders
Whereas aerosol therapy does not substitute for the managemental revisions required for horses with respiratory diseases, medical therapy is often indicated for patients in acute distress or to speed recovery. The medications which have been used may be classified in terms of their action on the respiratory system:

- Bronchodilators (β2 agonists, anticholinergics, xanthines derivatives);
- Prophylactic mast cell stabilisers;
- Anti-inflammatory substances (steroids and non steroids);
- Drugs acting on mucociliary clearance;
- Antibiotics

This classification includes the main drugs already used by inhalation in horses (Table 1). Other substances exist which are used by aerosol in human medicine but have not been yet developed in horses, or are currently administered only systemically. These will be summarised at the end of this article.
Bronchodilators

β2 agonists - These substances act by binding to adrenoreceptors on the smooth muscle cell surface, inducing relaxation of these muscles. They may also play a role in the control of mucus transport in the airways of patients suffering from obstructive lung disease. Some studies have demonstrated a stimulatory effect of β agonists on pulmonary mucociliary clearance in human medicine [28] and in horses [29]. The most important use of β2 agonists is to induce or to maintain bronchodilation in horses affected with heaves and small airway inflammatory disease. In heaves-affected ponies, aerosolized pirbuterol, at cumulative doses 2400-3200 µg, produced sweating, trembling and excitement [30]; however at a dose of 800 µg, its bronchodilator effects lasted for at least 30 min with minimal side effects. In heaves-affected horses, another study by Derksen et al., [25] concluded that pirbuterol could be inhaled via an MDI and caused bronchodilation at an optimal dose of 600 µg/horse without appearance of side effects. The duration of action was approximately 1 h. The same observation was reported after inhalation of 360 µg of albuterol sulfate [31,32]. On the other hand, contradictory results have been reported about the potential ability of inhaled albuterol sulfate to improve performance in healthy horses [33,34].

Anticholinergic drugs - These substances, acting as parasympatholytic agents, are competitive inhibitors of acetylcholine at its receptor sites [35]. The parent compound of this class of drugs is atropine. In the horse, systemic use of atropine has been shown to induce or maintain gastrointestinal stasis [36], increasing the risk of colic. Moreover, its duration of action is short [37]. At a dosage of 0.02 mg/kg body weight, atropine was found to cause identical changes in pulmonary parameters when given systemically or by inhalation, but because of its undesirable side effects (e.g., tachycardia, mydriasis, increased viscosity of bronchial secretions) it is not suitable as a long term therapeutic agent [38]. However, as a cholinergic component has been identified in the bronchospasm observed in equine heaves [39], atropine is used to treat punctually this kind of respiratory disorder. Ipratropium bromide, a compound chemically derived from atropine, is virtually free of central effects when aerosolized since, when given by this route, its rate of absorption from the airways is greatly decreased and its blood concentration is very low [40]. In heaves-affected horses, ipratropium bromide nebulisation causes bronchodilation lasting about 6 h at a dosage of 2 µg/kg body weight [19]. Dry powder inhalation of this agent has also been shown to improve pulmonary function of affected horses at the same dosage [41]. This substance may be potentially beneficial to treat airway inflammatory disease since there is some evidence that vagally mediated bronchoconstriction also occurs in this pathology [42].

| Table 1. Proposed doses of some drugs used for aerosol therapy in horses. |
|-----------------|-----------------|------------|----------|
| Class           | Substance       | Dose       | Frequency|
| Anticholinergic | Ipratropium bromide | 1 mg       | q 8h     |
| β2 Agonists     | Albuterol       | 720 mg     | q 3h     |
|                 | Clenbuterol     | 200 mg     | q 8h     |
|                 | Salmeterol      | 350 mg     | q 8h     |
| Mast Cells Stabiliser | Na Cromoglycate | 80 mg     | q 24h    |
| Corticosteroids | Budesonide      | 800 mg     | q 12h    |
|                 | Beclomethasone  | 500 mg     | q 12h    |
| Antibiotics     | Fluticasone     | 1 mg       | q 12h    |
|                 | Ceftiofur       | 250 mg     | q 12h    |
|                 | Gentamicin      | 250 mg     | q 12h    |
| Mucokinesis     | Acetylcysteine  | 1 g        | q 12h    |

The proposed drugs do not take into account whether these drugs have been approved for use in horses by the national authorities.

Xanthine derivatives - Theophylline and aminophylline are the best known xanthine derivatives. They are usually given orally or parenterally in horses. However, in human medicine some studies have demonstrated their efficacy when inhaled, although bronchodilation was less than that obtained after inhalation of β agonists [43,44]. They have an effect on
mucociliary clearance which has been attributed to stimulation of mucus transport in the central airways [45]. In heaves-affected horses, it appears that only 5% show a beneficial response to the administration of i.v. xanthine derivatives [37]. Another study determined correlation between plasma concentrations of i.v. theophylline and pulmonary mechanics in ponies with recurrent airway obstruction [46]. The authors concluded that theophylline was an effective bronchodilator at a plasma concentration of 59 µmol/l, but above 84 µmol/l, systemic side effects (i.e., excitement and tachycardia) appeared. Although xanthine derivatives appear to be effective as a bronchodilator in horses, there is an even narrower therapeutic margin than in man [47] and no evidence of effectiveness has been published concerning their aerosol use in the equine species.

**Mast Cell Stabilisers**

Sodium cromoglycate is believed to inhibit the release of chemical mediators from mast cells in bronchial smooth muscle, hence preventing the onset of bronchoconstriction [45]. Having no direct effects on bronchial smooth muscle and no direct antagonism against inflammatory mediators, sodium cromoglycate is mainly used prophylactically [48]. Nevertheless, if the drug reduces vagal bronchial afferent stimulation, it may reduce reflex bronchoconstriction and therefore decrease nonspecific bronchial hyperreactivity [49]. Various studies have tested the action of nebulised sodium cromoglycate in heaves-affected horses [50-52]. For example, nebulisation of 80 mg once daily for 1 - 4 days appears to prevent signs of heaves for up to 3 weeks after challenge exposure. However, another study failed to show significant prophylaxis even when horses were nebulised with up to 500 mg sodium cromoglycate for 2 consecutive days before barn exposure [18]. On the other hand, inhaled sodium cromoglycate was shown to be unable to prevent EIPH in racing quarter horses [53].

**Corticosteroids**

In human patients, inhaled corticosteroids are highly effective in controlling asthma [54,55]. They suppress asthmatic inflammation predominantly by reducing transcription of genes coding for inflammatory mediators and enzymes [56]. Drugs used (beclomethasone, betamethasone, triamcinolone, budesonide, fluticasone, flunisolide) exert a topical effect in the lungs but are inactivated when absorbed from the gut. The dose required and resultant plasma levels are low, and systemic side effects are, therefore, minimal [57,58]. In man, the principal side effects of aerosolized corticosteroids include oropharyngeal candidiasis, dysphonia and voice hoarseness. However, the use of spacers in combination with MDIs has been reported to reduce oropharyngeal deposition and hence also these side effects.

In horses suffering from lower airway disease, the improvement of clinical signs following systemic corticosteroid therapy is well known. Intramuscular injection of prednisolone over a period of 3 days decreased airway hyperreactivity following histamine inhalation challenge [59]. Undesirable side effects of the systemic administration of steroids (adrenal suppression, predisposition to laminitis and infections) are possible and these agents should be used at the effective lowest dose with the least frequency possible [60]. A study demonstrated that intramuscular injections of triamcinolone decreased airway obstruction in horses suffering from heaves but this was not significant for horses in which dyspnoea was not completely reversed by atropine [61].

Beclomethasone dipropionate is a common steroid used to treat human asthma [62]. It is available in horses by the mean of a MDI and, when administered at a dose of 3750 µg bid for a 2 week period via the Canadian Aeromask, it has been shown to reduce markedly respiratory dysfunction in heaves-affected horses [63]. Another study has shown that inhalation of large doses of beclomethasone is associated with a quickly-reversible suppressed adrenocortical function, similar to that one observed after parenteral administration of dexamethasone [64,65]. However the efficacy is similar and the side effects are less important if a lower dose is used (500 µg bid) [66].

**Drugs Acting on Mucociliary Clearance**

The rate of removal of mucus from the airways is determined by a number of factors, such as mucus viscosity, the amount of mucus produced, and ciliary activity. These processes may be influenced by a variety of diseases including heaves [67]. Mucokinetic drugs are used in the treatment of equine pulmonary diseases. There is, however, still limited scientific evidence as to the clinical value of many of these agents both in man and horses, even though it has been shown that several agents significantly increase mucociliary clearance. Mucociliary drugs can be divided into 5 groups according to their mechanisms of action:

- Mucolytic drugs (sterile water, sterile saline, acetylcysteine, sodium bicarbonate, propylene glycol);
- Surface-acting drugs (glycerol, ethyl alcohol);
- Bronchomucotropic agents (expectorants such as bromhexine, potassium iodide, etc);
- Cilia augmentors (β sympathomimetics);
- Bronchodilators (β sympathomimetics, xanthines).

Most of the effective mucolytic and surface-acting agents and some bronchomucotropic drugs must be given by aerosol to
Antifungal Agents
EIPH, frusemide has been reported to reduce the volume of haemorrhage [1]. Bronchodilation lasting about 5 h and the effect appeared to be mediated through prostanoids [80]. In horses suffering from heaves, i.v. injection of frusemide (1 mg/kg body weight) caused it to be mixed with 10% ethanol before use for aerosol therapy. Its clinical efficacy has been demonstrated in bovine bronchopneumonia [71] but not yet in horses. In fact, there appears to be no published studies on the efficacy of antibiotic inhalation in mature horses. It should mentioned that the pollution of the surrounding air must be taken into account before nebulizing horses with antibiotics.

Other Agents
Nonsteroidal Anti-Inflammatory Drugs - Recent studies suggest that nonsteroidal anti-inflammatory compounds (nimesulide, indomethacin and acetylsalicylic acid) given by aerosol may affect lung inflammation, as demonstrated in a study in which guinea-pigs were protected from immune bronchocstriction [72]. Clinical signs of heaves are the result of airway obstruction and pulmonary inflammation [73] and control of the inflammatory response is an important objective of therapy in heaves as well as in some other respiratory disorders. However, i.v. administration of flunixin meglumine, a cyclooxygenase inhibitor, to heaves-affected ponies did not modify the degree of airway obstruction after barn exposure [74]. There appear to have been no studies published concerning the efficacy of non steroid aerosols in horses.

Frusemide - In man, inhaled frusemide is known to prevent asthma induced by exercise [75] and to protect against allergen-induced asthmatic reactions [76]. In horses, frusemide is a potent natriuretic-diuretic agent that can also depress the response of smooth muscle to some agonists and nerve stimulation [77]. Its attenuation of pulmonary vascular pressures is mainly attributable to a diuresis-induced decrease in plasma volume and associated reduction in venous return. However, frusemide may also increase production of prostaglandins, which may result in increased vascular capacitance and, therefore, decreased venous return to the heart [78]. It has been shown that inhaled and i.v. frusemide (1 mg/kg body weight) has a bronchodilator effect when given to ponies with airway obstruction [79]. In horses suffering from heaves, i.v. injection of frusemide (1 mg/kg body weight) caused bronchodilation lasting about 5 h and the effect appeared to be mediated through prostanoids [80]. In horses suffering from EIPH, frusemide has been reported to reduce the volume of haemorrhage [1].

Antifungal Agents - Although iodides have long been used for their apparent secretolytic action to aid expectoration, their use in horses for this purpose has not been critically evaluated. When administered systemically, they have no anti-inflammatory or bronchodilator effects. The respiratory epithelium can actively transport iodide ions into the airway lumen, and iodide can increase proteolytic digestion of mucus by enzymes present in purulent sputum [60]. Nevertheless, their exact mode of action and efficacy remain uncertain. It is worth noting that amphotericin nebulisation has been advocated in the treatment of equine fungal pneumonia [81] and that polyvidone iodine 1% nebulisation is used by some practitioners to treat fungal infections in the airways.

Other Agents - A variety of agents is used to treat several diseases in human medicine. For instance, anti-mediator drugs (e.g. histamine, serotonin and leukotriene antagonists, platelet-activating factor antagonists, thromboxane synthetase inhibitors), cytokines, detergents and antiviral drugs are under experiment. As similarities exist between a number of human and equine respiratory disorders, some treatments may offer new perspectives for therapy of horses. However, all species-to-species extrapolation should be validated by specific studies in the targeted species. Inhalation is also used in horses for diagnostic purposes. Aerosolized agonists such as histamine, methacholine, citric acid, mould antigens, etc., are used in order to evaluate airway reactivity [82-84]. Radioaerosols are also used for the diagnosis of ventilation to perfusion mismatching [85]. In the future, cellular, molecular and gene therapies could be provided to the airway epithelium by inhalation of vectors such as cationic agents and non pathogen viruses [86].

Conclusions
Aerosol delivery of bronchodilators and corticosteroids could become the most common way to treat respiratory disorders like heaves. Future research should determine the most useful drugs for other equine respiratory diseases. An understanding of aerosol techniques and patho-physiological modifications of the airways in disease would also greatly facilitate the use of
inhalation therapy by equine clinicians. Nevertheless, with the substances that have already been tested, and with the devices currently available (or to be available soon), we have an efficacious therapeutic method to contribute to treat some respiratory disorders encountered in horses. Since most respiratory disorders require frequently-repeated drug administrations, the use of aerosol administration allows owners or grooms to continue the treatment without requiring the veterinarian to be present, so that the horse profits by the use of a highly appropriate treatment.

References

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