Evidence-based Clinical Question

Does clenbuterol positively affect racing horses?

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Introduction

Clenbuterol, a β2-sympathomimetic agent, is a synthetic hormone with similar physiological functions to the catecholamines, epinephrine and norepinephrine. Clenbuterol is one of a large group of compounds that are selective β2-adrenergic agonists. Other drugs in this class include albuterol (salbutamol), pirbuterol and fenoterol. At low doses, clenbuterol preferentially activates β2-adrenoceptors, but at higher doses it begins to activate β1-adrenoceptors (Robinson 2000).

Clenbuterol is sometimes used for its bronchodilatory effect in horses suffering from chronic obstructive pulmonary disease (COPD or ‘heaves’) and other forms of respiratory distress. Its main action in the lung is relaxation of airway smooth muscle. Clenbuterol is also widely believed to have efficacy as bronchodilator in normal racing horses, and in some countries, it has been common to use it illegally in an effort to improve air delivery to the lungs (Slocombe et al. 1992). Because it is both a bronchodilator and a repartitioning agent, i.e. it redirects dietary energy away from fat deposition in the direction of lean muscle tissue production, clenbuterol has been used in an effort to enhance performance in horses.

Clenbuterol and the respiratory system

Clenbuterol is used as a bronchodilator to relieve bronchospasm. The main action of clenbuterol in the equine lung is relaxation of airway smooth muscle. When the drug binds to β2-adrenoceptors, it activates adenyl cyclase, which leads to an increase in the intracellular concentration of the second messenger cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). In the tracheobronchial tree (as well as in the uterus), β2-agonists, cAMP and PKA inhibit smooth muscle contraction by opening K+ channels and downregulate myosin light chain kinase activity (Robinson 2000).

Acute administration of clenbuterol to healthy horses does not improve pulmonary function during exercise. Following clenbuterol administration (0.8 µg/kg bwt i.v.) in healthy horses, nonelastic resistance of the lung or pulmonary resistance significantly decreased, with 33.6% reduction at 10 min post clenbuterol, and a return to normal values after 3 h (Shapland et al. 1981). Premedication of normal racehorses with i.v. clenbuterol at the recommended dosage does not alter pulmonary mechanical and gas exchange properties during exercise (Slocombe et al. 1992). Likewise, i.v. administration of clenbuterol to Thoroughbred horses 30 min before exercising on a treadmill does not improve oxygen consumption or cardiovascular function. Because the plasma concentration resulting from the same oral dose would be lower, it is even less likely that acute oral administration (using the currently available veterinary product) would have any effect on oxygen consumption (Robinson 2000). Thus, while clenbuterol may help return the diseased horse to normal function, it fails to enhance performance demonstrably in healthy individuals, at least by standard statistical analyses.

Clenbuterol and muscle

Chronic clenbuterol administration is believed to be ergogenic through the production of increased muscle mass, but paradoxically, this effect appears to impair exercise capacity. Clenbuterol results in significant repartitioning in horses when administered at the recommended doses, both alone and in combination with exercise. When caloric intake is controlled, exercise alone and clenbuterol administration alone result in a decrease in total body fat mass and percentage body fat in healthy horses, and the combination of exercise and clenbuterol administration has an additive effect on these parameters (Kearns et al. 2001). Both exercise and clenbuterol administration increase fat-free body mass, but the combination of exercise and clenbuterol administration seemed to attenuate partially the effect of clenbuterol alone on treatment-induced increases in fat-free body mass. Clenbuterol decreases the time to fatigue in horses (Kearns and McKeever 2002) and rats (Suzuki et al. 1997); i.e. animals treated with clenbuterol fatigue sooner than animals without clenbuterol treatment. Treated horses developed a power output 11% greater than the control group, and the muscle mass was approximately 16% greater. However, the power...
output expressed per gram of muscle was approximately the same in both groups. Since the relative power output in both groups was the same, a difference in rate of fatigue can be attributed to some inherent change within the muscle.

The mechanism of increased fatigueability secondary to chronic clenbuterol administration is unclear. The administration of clenbuterol at ≥1 µg/kg bwt in rats induces apoptosis in skeletal muscle (Burniston et al. 2005). In addition, there was a cumulative myocyte death over 8 days after administration of clenbuterol at a 48 h interval in rats. Apoptosis alone was observed at low clenbuterol doses; in most cases apoptotic myocytes lyzed and became necrotic, and the magnitude of necrosis was greater than that of apoptosis. Clenbuterol provokes a shift in myosin heavy chain (MHC) composition toward the fast-twitch isoforms in the soleus muscle of rats (Dodd et al. 1996) and in middle gluteal muscles of Standardbred mares (Beekley et al. 2003). This study also suggested that aerobic exercise might not be able to reverse these effects. Given that fast-twitch fibre (i.e. Type II muscle fibres) are more easily fatigued than Type I muscle fibres, it is likely that these MHC shifts are detrimental to prolonged exercise performance.

**Clenbuterol and cardiac function**

Undesirable effects of chronic clenbuterol administration on cardiac function may also contribute to impaired athletic performance, but the current data are not consistent. In one study, no changes were found in heart rate response to exercise 2 h after clenbuterol administration (Kallings et al. 1991). In addition, clenbuterol treatment did not affect blood lactate concentration or arterial oxygen tension during exercise. However, in another study, chronic clenbuterol administration caused cardiac remodelling and adversely affected cardiac function (Sleeper et al. 2002). Horses treated with clenbuterol had substantially elevated cardiac output (Q) and stroke volume (SV) immediately after a standardised exercise test when compared to untreated horses, suggesting lower cardiovascular efficiency for a given workload. After 8 weeks, horses receiving clenbuterol, with or without concurrent exercise training, had a significantly elevated SV immediately after maximal exercise due to increased left ventricular dimension (LVD). Other increases included intraventricular septal wall thickness (IVS) at end diastole, IVS at end systole immediately after exercise, and left ventricular posterior wall systolic thickness. Absolute aortic root diameter immediately after exercise was larger in both horses with exercise and without exercise after treatment with clenbuterol, suggesting increased risk of aortic rupture. Chronic clenbuterol treatment has been shown to cause cardiac hypertrophy in many other species, including rats (Petrou et al. 1995; Wong et al. 1998; Duncan et al. 2000), and mice (Cubria et al. 1998), in some cases associated with evidence of myocardial damage (Cubria et al. 1998, Duncan et al. 2000). Although not conclusive, the current data suggest that chronic clenbuterol administration may have adverse effects on cardiac function in healthy horses.

**Clenbuterol and performance**

Exercise training is expected to increase maximal aerobic capacity (VO\textsubscript{2max}) in horses, and this increase is associated with increased plasma volume (presumably permitting greater cardiac output). However, even minimal therapeutic concentrations of clenbuterol adversely affect aerobic performance, high-intensity exercise capacity and the horse’s ability to recover from exercise (Kearns and McKeever 2002). Horses treated with clenbuterol and exercise training demonstrated a reduction in VO\textsubscript{2max} (-10%) and plasma volumes (-10%). Interestingly, no significant changes in VO\textsubscript{2max} (-3.5%) or plasma (3.0%) of the clenbuterol-treated horses without exercise training were found, suggesting the antiergogenic effect of chronic clenbuterol administration in athletic horses is a result of interaction with exercise.

**Conclusion**

Clenbuterol has effects in multiple body systems and tissues directly relevant to exercise performance, including the respiratory system, cardiovascular system, and skeletal muscle. Some of these effects, such as bronchodilation and increased muscle mass, could potentially be ergogenic. However, numerous studies in horses have failed to demonstrate a clear ergogenic benefit of clenbuterol, and in some cases, have demonstrated impaired exercise capacity. Thus, the current body of evidence supports the use of clenbuterol only as a specific treatment for horses with chronic airway disease, but not in healthy horses as a performance-enhancing drug.

**References**


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