Performance-enhancing effects of non-selective endothelin receptor antagonist☆,☆☆,★

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Endothelin receptors antagonists (ERA) are a class of vasoactive drugs that blocks endothelin receptors and may induce vasodilatation, cardiac inhibition and improve hemodynamics [1]. Several ERA have been developed for the treatment of pulmonary arterial hypertension (PAH) [2], with anecdotal reports of the use of ERA among athletes to counteract exercise-induced rise in pulmonary vascular pressures and increase exercise performance [3]. Bosentan, potent oral non-selective ERA, has been newly approved for the treatment of PAH, with drug demonstrated efficacy on exercise capacity in patients with PAH [4]. Experimental studies in healthy volunteers indicated that bosentan might positively influence exercise performance in hypoxic conditions [5]. Yet, there is a paucity of information available regarding the effects of bosentan on exercise capacity in healthy trained subjects in normoxic conditions. The possible effects of prolonged bosentan administration on exercise performance may be relevant in terms of its possible fraudulent utilization to influence athletic performance, raising the difficult question of whether bosentan might be considered as prohibited substance in athletes. Therefore, the main aim of the present study was to investigate in a double-blind, placebo-controlled, randomized trial whether oral intake of bosentan administered for 8 weeks in newly approved doses (250 mg per day of bosentan: maximum authorized dose for PAH treatment) improved exercise performance in healthy athletes.

Twenty young male and female college athletes (aged 21.3 ± 1.5 year) gave written informed consent to participate in this study. The mean physical characteristics of participants were: weight 70.6 ± 10.1 kg, height 175.3 ± 12.4 cm, and body fat 20.3 ± 5.8%. Approval of the IRB was obtained with all procedures performed in accordance with the Declaration of Helsinki. Participants were randomized according to a computer-generated randomization list in a double-blind design to receive two randomly assigned trials: first group was administered with 250 mg of bosentan per day in a single dose (BOS); second group was administered with placebo (PLA; cellulose). Sample size (10 subjects per group) was calculated according to 0.80 power and 5% alpha risk to detect significant difference in maximal oxygen consumption (VO_{2max}). Administration period lasted for 8 weeks. The participants visited laboratory on six occasions: before starting receiving the intervention (baseline) and after one, two, four, six and eight weeks during the intervention period. Fasting blood samples were withdrawn for the measurement of blood count, glucose, lipids, serum liver and muscle enzymes, free and total testosterone, cortisol and dehydroepiandrosterone sulfate. Exercise performance assessment included isometric and isotonic strength [6], anaerobic power and capacity [6], and running aerobic performance [7], with gas-exchange data collected using a breath-by-breath metabolic system (Quark CPET, Cosmed, Italy). The data were expressed as the mean ± standard deviation. SPSS 21.0 software was used for statistical analysis. A value of $P < 0.05$ was considered statistically significant.

Table 1 presents exercise performance indicators during the study, with no significant differences existed between group responses during the intervention period ($P > 0.05$). VO_{2max} increased for 1.8 ml/kg/min (95% CI = −5.5–9.1 ml/kg/min) from before to after administration in BOS-administered participants, while elevated by 1.7 ml/kg/min (95% CI = −4.5–7.9 ml/kg/min) after eight weeks of administration in the placebo group.

No significant differences existed for hematological indices, blood glucose and lipids between group responses over time of intervention ($P > 0.05$) (Table 2). It seems that bosentan significantly elevated liver enzymes ($P < 0.0001$), while other clinical enzymes were not affected by intervention. Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (gamma-GT) were elevated by 60.5 IU/L (95% CI = 43.7–77.1 IU/L), by 30.6 IU/L (95% CI = 15.6–45.6 IU/L), and by 34.5 IU/L (95% CI =23.8–45.2 IU/L) after eight weeks of administration in BOS group, respectively. No significant differences were found between the groups for serum free testosterone ($P = 0.87$), total testosterone ($P = 0.90$), cortisol ($P = 0.15$), and dehydroepiandrosterone sulfate ($P = 0.57$).

Several RCTs have shown improvement in exercise capacity, hemodynamics, and electrocardiographic and Doppler variables after ERA treatment in PAH patients [8]. Furthermore, bosentan restored 30% of the hypoxia-induced decrease in VO_{2max} when administered twice a day for 3 days, 62.5 mg on the first day and 125 mg on the next 2 days [5]. In the present study we found that bosentan did not affect major indicators of anaerobic and aerobic performance, with similar time to exhaustion, oxygen uptake outcomes and running velocities between the groups during the study. Both groups experienced an increase in VO_{2max} after 8 weeks of administration, yet gains are similar and could be attributed to exercise training rather than intervention administered. It seems that the possible ergogenic effect of bosentan on exercise performance in healthy normoxic subjects is highly unlikely.

☆ NOTE: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
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Table 1
Exercise performance indicators during the study (values are mean ± SD).

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8
Total handgrip strength (kg)						
Placebo	82.9 ± 24.7	83.0 ± 25.7	85.1 ± 25.1	83.9 ± 25.0	83.6 ± 24.9	82.3 ± 22.3
Bosentan	92.5 ± 26.9	94.4 ± 26.4	96.1 ± 27.7	96.7 ± 30.1	96.0 ± 28.7	95.4 ± 25.0
Bench press (no. of repetitions)						
Placebo	18.7 ± 10.0	18.4 ± 8.5	20.1 ± 10.0	19.8 ± 10.3	19.7 ± 10.0	18.6 ± 9.8
Bosentan	18.8 ± 11.4	19.3 ± 11.9	23.1 ± 13.9	23.6 ± 14.4	24.2 ± 14.9	22.6 ± 12.3
Leg press (no. of repetitions)						
Placebo	29.6 ± 15.7	29.4 ± 15.5	30.3 ± 14.7	29.8 ± 14.5	32.3 ± 14.9	32.2 ± 13.3
Bosentan	29.6 ± 10.3	31.4 ± 12.0	31.4 ± 12.0	34.0 ± 13.5	37.7 ± 16.9	31.0 ± 11.7
Maximal anaerobic power (W/kg)						
Placebo	13.2 ± 1.8	13.4 ± 2.1	13.7 ± 2.1	13.6 ± 1.9	13.6 ± 1.9	13.6 ± 1.8
Bosentan	13.2 ± 1.6	13.6 ± 1.7	13.6 ± 1.7	13.5 ± 1.8	13.3 ± 1.9	13.5 ± 1.7
Relative peak power output (W/kg)						
Placebo	10.9 ± 1.6	10.6 ± 1.4	10.7 ± 1.4	10.7 ± 1.5	10.4 ± 1.3	10.4 ± 1.3
Bosentan	10.8 ± 1.5	11.1 ± 1.2	10.8 ± 1.2	10.7 ± 1.2	10.5 ± 1.2	10.4 ± 1.2
Anaerobic capacity (W)						
Placebo	895.2 ± 246.1	725.3 ± 218.8	738.8 ± 216.8	735.1 ± 218.5	719.3 ± 210.4	716.9 ± 196.7
Bosentan	968.2 ± 312.4	816,5 ± 249.8	811.7 ± 260.5	802.5 ± 256.0	795.7 ± 260.2	791.3 ± 251.8
Time to exhaustion (sec)						
Placebo	498.5 ± 104.0	487.5 ± 83.9	498.3 ± 81.2	501.7 ± 79.7	492.8 ± 74.0	486.1 ± 74.5
Bosentan	490.5 ± 92.1	484.0 ± 91.6	514.4 ± 106.8	501.7 ± 105.8	518.3 ± 101.7	510.6 ± 103.0
Oxygen uptake at critical velocity (ml/kg/min)						
Placebo	30.5 ± 2.8	31.7 ± 3.1	32.0 ± 3.6	32.4 ± 4.2	32.4 ± 4.8	32.3 ± 5.3
Bosentan	32.3 ± 4.4	33.4 ± 5.1	34.4 ± 5.1	34.9 ± 3.8	34.9 ± 4.5	33.8 ± 4.6
Ventilatory threshold (% of peak oxygen uptake)						
Placebo	78.4 ± 8.3	80.6 ± 7.8	81.9 ± 4.7	80.4 ± 5.7	80.9 ± 4.2	81.6 ± 4.2
Bosentan	79.0 ± 4.8	81.8 ± 4.0	82.0 ± 5.4	80.9 ± 3.6	82.2 ± 3.9	82.7 ± 4.7
Velocity at ventilatory threshold (km/h)						
Placebo	12.9 ± 1.3	12.9 ± 1.3	13.2 ± 1.5	13.3 ± 1.4	13.4 ± 1.3	13.4 ± 1.2
Bosentan	11.8 ± 1.3	12.9 ± 1.0	13.0 ± 1.1	13.1 ± 1.3	13.3 ± 1.2	13.1 ± 1.4
Peak velocity (km/h)						
Placebo	15.0 ± 1.7	15.0 ± 1.4	15.1 ± 1.4	15.2 ± 1.0	15.6 ± 1.1	15.6 ± 1.1
Bosentan	14.2 ± 1.8	15.1 ± 1.5	15.2 ± 1.4	15.5 ± 1.4	15.7 ± 1.4	15.0 ± 1.5
Peak oxygen uptake (ml/kg/min)						
Placebo	43.7 ± 5.9	44.3 ± 6.1	44.8 ± 6.6	44.5 ± 5.9	45.2 ± 6.6	45.4 ± 7.0
Bosentan	44.3 ± 7.7	44.8 ± 7.2	45.3 ± 7.2	46.0 ± 7.6	46.0 ± 7.7	46.1 ± 7.4

Note No significant differences were found between the groups ($P > 0.05$).

In clinical studies, bosentan caused at least 3-fold upper limit of normal elevation of liver aminotransferases in about 11% of patients [9]. Because these changes are a marker for potential serious hepatotoxicity, FDA requires monthly monitoring of serum aminotransferase levels prior to initiation of treatment and then monthly. For the present study, we noted similar changes in liver enzyme profiles in participants administered with non-selective ERA. Bosentan induced elevation in AST for 3.4 times, ALT for 2.3 times and gamma-GT for 3.2 times after 8 weeks of administration, which may indicate liver cellular damage or necrosis.

Several studies demonstrated interaction between non-selective ERA and steroid hormones in the patients with PAH [1,8,10]. It seems that bosentan may activate the human pregnane X receptor (PXR), also known as the steroid and xenobiotic sensing nuclear receptor, with activation, could affect the concentration and activity of sex steroids [10]. If proven, the potential of bosentan to affect the serum level of exercise-related steroid hormones may be highly relevant in terms of their possible ergogenic impact in sport. For the present study, we found no significant effect of 8-week bosentan administration on serum steroid concentration in young, healthy men and women. The results indicate no occurrence of anabolic response during bosentan administration.

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