Efficacy of GBT440 to left-shift the oxy-hemoglobin dissociation curve in healthy individuals and preserve arterial saturation during submaximal hypoxic exercise

Stewart. Glenn, Cross. Troy, Chase. Steven, Isautier. Jennifer, Joyner. Michael, Curry. Timothy, Vlahakis. Nicholas, Dufu. Kobina, Johnson. Bruce

Mayo Clinic, Rochester, USA; Global Blood Therapeutics, San Francisco, USA

Introduction

Numerous conditions can cause hypoxia-induced cardiopulmonary perturbations that are associated with the degree of arterial oxygen desaturation. Global Blood Therapeutics (GBT) has developed an allosteric modulator of hemoglobin (GBT440) that increases the affinity of hemoglobin for oxygen and left shifts the oxy-hemoglobin dissociation curve.

Accordingly, this study investigated the efficacy of GBT440 to preserve arterial oxygen saturation while exercising during acute hypoxia.

Methods

Eight subjects completed a submaximal cycling test (60W) under normoxic (fiO2: 0.21 %; O2 partial pressure: 144 mmHg) and hypoxic (fiO2: 0.12 %; O2 partial pressure: 82 mmHg) conditions before (D1) and after (D15) 14 days of oral GBT440 supplementation (Figure 1).

At rest (stationary on the cycle-ergometer) and during exercise, oxygen consumption (VO2), heart rate (HR) and cardiac output (Q) were measured non-invasively, while arterial blood pressure (MAP), oxygen partial pressure (PaO2) saturation (SaO2) and content (CaO2) were measured invasively.

Figure 1

This study (GBT440-0111) was funded and sponsored by Global Blood Therapeutics

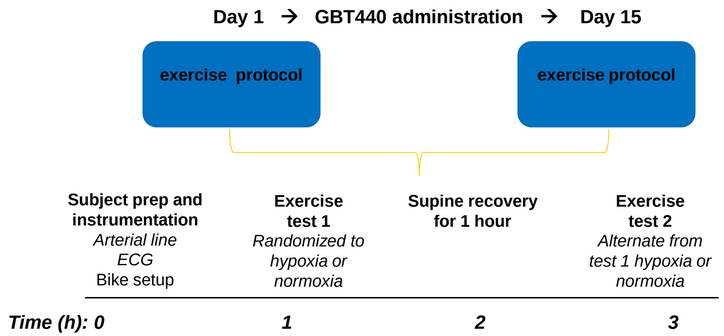

Figure 1. Schematic of study design.

Results

Fourteen days of GBT440 supplementation left-shifted the oxy-hemoglobin dissociation curve (p50; D1: 28.3 ± 0.7 mmHg vs D15: 26.0 ± 0.4 mmHg, $p<0.05$).

Under normoxic and hypoxic conditions, VO2, HR, Q and MAP were similar on D1 and D15 during submaximal exercise (Table 1).

Under normoxic conditions PaO2, SaO2 and CaO2 were similar on D1 and D15 at rest, while PaO2 and SaO2 were higher during exercise (Figure 2).

Under hypoxic conditions PaO2, SaO2 and CaO2 were higher on D15 than D1, both at rest and during exercise (Figure 2).

Table 1

Pulmonary gas exchange and hemodynamic variables during submaximal exercise

	Normoxia Day 1 vs Day 15	Hypoxia Day 1 vs Day 15
Submaximal Exercise (60 watts)		
Oxygen consumption, ml/min	1218±76 vs 1332±90	1263±69 vs 1261±67
Heart rate, beats/min	106±5 vs 112±6	121±5 vs 125±6
Cardiac output, L/min	13.3±0.5 vs 13.6±0.9	15.6±0.7 vs 16.6±1.1
Mean arterial pressure, mmHg	100±3 vs 103±5	107±4 vs 104±6
Arterial saturation, %	95.2±0.4 vs 96.6±0.3*	73.6±2.5 vs 84.8±2.7*

Data are mean ± SEM. *Significantly different to Day 1 ($p < 0.05$).

Conclusions

Oral administration of GBT440 caused a left shift in the oxy-hemoglobin dissociation curve and improved arterial saturations during submaximal exercise. This effect was more pronounced during submaximal hypoxic exercise, when arterial desaturation typically occurs.

Accordingly, GBT440 improves arterial oxygen saturation during acute exposure to hypoxia and may be beneficial for patient groups where (exercise) hypoxemia is present.

Figure 2

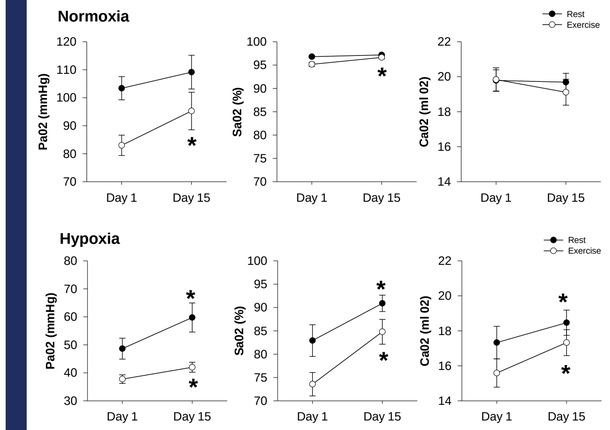

Figure 2 Arterial oxygen partial pressure (PaO2) saturation (SaO2) and content (CaO2) measured during normoxia (top panels) and hypoxia (bottom panels) before (Day 1) and after 14 days of supplementation with GBT440 (Day 15). * Significantly different to Day 1 ($p < 0.05$).