Effect of GBT440, an R-state stabilizer of hemoglobin, on hypoxic maximal exercise

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

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

Introduction

Arterial hypoxemia occurs in patho-physiologic states such as idiopathic pulmonary fibrosis. The reduced loading of oxygen onto hemoglobin impairs exercise capacity and quality of life, and may be related to the development of symptoms.

Left shifting the oxygen dissociation curve can improve arterial oxygen saturation under hypoxic conditions; however, it's unclear how this may affect exercise capacity.

Methods

Eight healthy subjects (5M/3F, Age: 36±7y, BMI: 24±2kg·m^{-2}, $VO_{2,\ peak}$: 49±2ml·kg^{-1}·min^{-1}) performed an incremental exercise test to exhaustion under hypoxic (12.5% O_2) conditions before and after oral ingestion of 900mg of GBT440 per day for 14 days.

During exercise, pulmonary gas exchange was measured continuously, arterial blood gases were assessed every 3 min and cardiac output was measured using a previously validated open circuit acetylene technique.

Results

- Fourteen days of GBT440 administration left-shifted the oxy-hemoglobin dissociation curve (p50; Day1: 28.3 ± 0.7 mmHg vs Day15: 26.0 ± 0.4 mmHg, p<0.05).
- Subjects reached a similar maximal work rate and oxygen consumption on Day 1 and Day 15. All ventilatory and hemodynamic parameters were similar throughout exercise and at peak on Day 1 and Day 15. (Table1).
- Throughout the incremental exercise test and at max, arterial oxygen saturation was systematically higher on Day 15 than Day 1, while oxygen consumption was unchanged (Figure 2).

Conclusions

GBT440 improved arterial oxygen saturation as well as oxygen content during maximal hypoxic exercise, while maintaining the extraction of oxygen at the tissue (AVO_2 difference 11.5 vs 11.2 ml/100 Day 1 vs 15). Maximal VO_2 was not reduced, and subjects did not perceive a difference in exercise intensity or dyspnea.

These results suggest that GBT440 could be an effective measure to improve oxygen saturation with rapid exposure to hypoxic conditions; however further studies would need to be pursued to determine the impact of the drug on more chronic forms of hypoxia, such as chronic disease conditions.

Purpose

We investigated the effect of GBT440 on maximal exercise under hypoxic conditions in healthy subjects and hypothesized that GBT440 would improve oxygen saturation without negatively impacting maximal exercise capacity.

Figure 1

Figure 1. Schematic of study design.

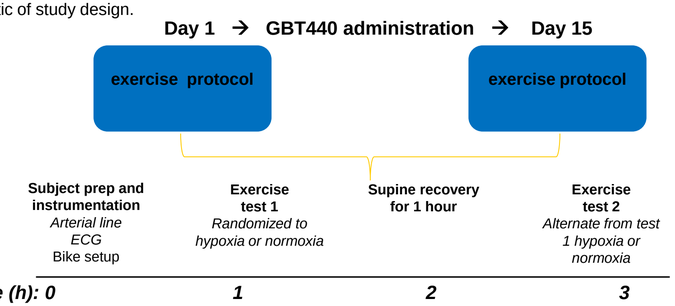

Table 1

	Day 1	Day 15
Peak exercise values		
Work rate, watts	208±10	208±10
Time to exhaustion, min	16.6±0.5	16.0±0.6*
Oxygen consumption, ml/min	2596±140	2480±153
Ventilation, L/min	128±9	127±9
Heart rate, beats/min	171±2	173±2
Cardiac output, L/min	23±2	24±3
Mean arterial pressure, mmHg	129±4	129±4
Arterial saturation, %	70±3	78±2*
PaO2, mmHg	41±2	45±2*
CaO2, mlO2/dL	15.5±0.7	16.8±0.5*
Lactate, mmol/L	15.6±1.7	14.3±1.3
pH	7.33±0.03	7.32±0.02
Dyspnoea, 0-10	9±0.4	9±0.4
Rating of perceived exertion, 6-20	19±0.3	19±0.5

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

Figure 2

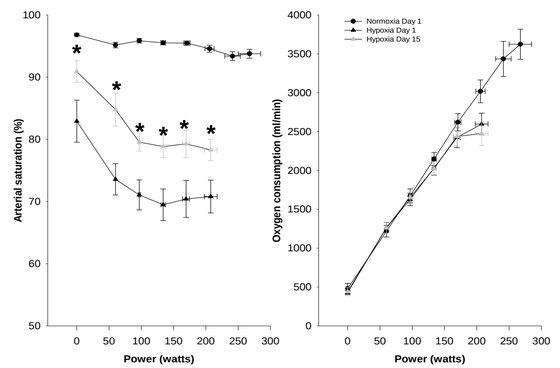

Figure 2 Oxygen consumption and arterial oxygen saturation during incremental exercise at baseline (Normoxia Day 1 and Hypoxia Day 1) and after 14 days of GBT440 administration (Hypoxia Day 15). *Significantly different to Hypoxia Day 1 (p < 0.05).

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