BACKGROUND

Sickle cell disease (SCD) is characterized by hemolytic anemia, vaso-occlusion, and progressive organ damage. The underlying mechanism of SCD is the polymerization of sickle hemoglobin (HbS) that occurs when sickle erythrocytes are deoxygenated in microcirculatory beds leading to acute painful crises.

OBJECTIVES

To establish the implication of increased Hb-O2 affinity in SCD during normoxia and hypoxia.

RESULTS

• In vitro modification of blood samples (20% hematocrit) with voxelotor or GBT1118 resulted in a dose-dependent left-shift of the oxygen equilibrium curves to the same degree by the 2 compounds. Results indicate that increases in Hb-O2 affinity with voxelotor are of similar potency to voxelotor (Figure 1).

• Time-concentration profiles following single oral doses (10 mg/kg) in SCD mice indicate GBT1118 is of higher and longer half-life compared with voxelotor in SCD mice (Figure 1B).

• In SCD, a pharmacologically mediated increase in Hb-O2 affinity preserves cardiovascular function and maintains MAP and HR without any hypoxic tolerance in SCD mice (Figure 1).

• Blood gas analysis shows that the pharmacological increase of Hb-O2 affinity:
  - Resulted in increased arterial O2 content under normoxic (21% O2) and hypoxic (10% O2) conditions (Figure 3A).
  - Resulted in increased venous O2 content under normoxic (21% O2) and hypoxic (10% O2) conditions (Figure 3A).
  - Did not limit systemic O2 extraction in SCD mice (Figure 3C).

• Brain oxygen measurements indicate that the pharmacological increase of Hb-O2 affinity:
  - Did not decrease brain tissue pO2 under normoxic (21% O2) conditions (Figure 4A).
  - Significantly increased brain tissue O2 tension under hypoxic conditions (10% O2) (Figure 4B).
  - Significantly reduced brain tissue hypoxia during exposure of SCD mice to 10% O2 (Figure 4C).

CONCLUSIONS

• Under hypoxic conditions, the pharmacological increase of Hb-O2 affinity improves cardiac, cerebral, and multi-organ perfusion in SCD mice (Figure 6).

• A pharmacological increase of Hb-O2 affinity does not impair oxygen extraction by tissues including the brain under either normoxic or hypoxic in SCD mice.

• A pharmacological increase of Hb-O2 affinity led to increased brain O2 content, O2 carrying capacity, and O2 delivery in SCD mice.

REFERENCES


