Altitude-Induced Changes to the Blood Brain Barrier's Permeability Adversely Impact Patient Safety in Aeromedical Evacuation

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ABSTRACT

INTRODUCTION: The cumulative effects of flight during aeromedical transport are of great interest to all nations engaged in contingency operations, and especially to the U.S. Air Force, the sole provider of U.S. aeromedical evacuations (AE). Key factors affecting clinical outcome include the optimal choice of pain management strategies, the relative efficacy of medications en route and, most importantly, the safety of such medications; AE may have an adverse impact on these factors. Here, we investigated the potential for neuroactive and non-neuroactive drugs to enter the brain at common AE cabin altitudes.

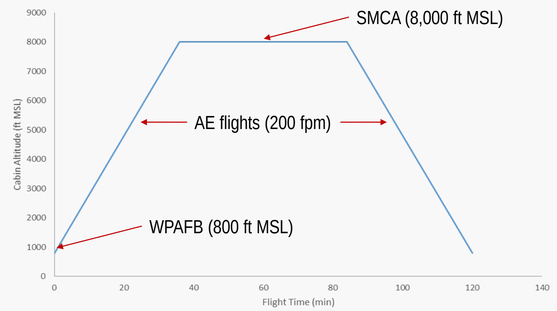
METHODS: The human blood brain barrier was simulated using porcine brain extracts in the parallel artificial membrane permeability assay (PAMPA) arrangement. Multi-well PAMPA plates were exposed to a simulated cabin altitude of 8,000 ft mean sea level (MSL) in a hypobaric chamber with an identical plate held constant at 800 ft MSL (Wright-Patterson AFB, OH). Drugs were added to a single side of the membrane prior to exposure, and drug concentrations post-exposure were analyzed using liquid chromatography mass spectrometry. Flight profiles represented 2-h and 12-h AE missions.

RESULTS: The average drug concentration ratio between altitude and ground on the brain side for the 2 h flight was 0.61±0.49 versus an average ratio of 1.25±0.37 after the 12 h flight (n=17 drugs, p=0.00062). After the 2 h flight, only 3 drugs had altitude-to-ground ratios above 0.8; whereas, after the 12 h flight only 1 drug was below 0.8 and 13/17 (76%) were above 1.

DISCUSSION: The altitude-induced permeability increase for numerous drugs that are not normally neuroactive poses a clear safety risk. Furthermore, a potentially even greater threat to patient safety is posed by pharmaceuticals that are normally active in the brain, but are dosed at low levels to account for their activity. When present at higher levels, these drugs can potentially slow, or even damage, brain function. The pilot study here demonstrates that a systematic investigation of additional cabin altitudes and more drugs will better define drug effects at altitude, potentially improving patient outcomes during and after transport. Such outcomes can be realized through development of a clinician-friendly "app" for use in routine and emergency transports.

MATERIALS AND METHODS

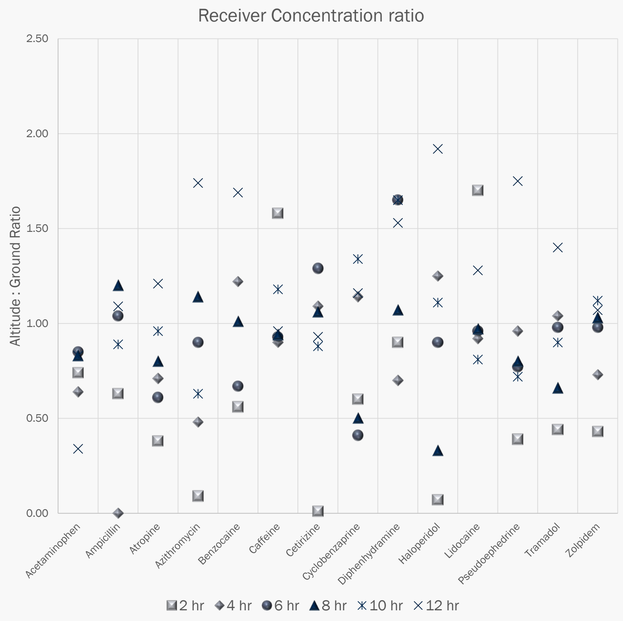
- Drug sources: Sigma Aldrich/SelleckChem, dry powder or 10 mM in DMSO
  - Dissolved powders in DMSO to 10 mM
  - Diluted drugs to 100 μM in PBS
- PAMPA Methods
  - Millipore MultiScreen-IP PAMPA & receiver plates (Thermo Fisher)
  - Total Brain Lipid Extract (Avanti Polar Lipids)
  - 4 μL lipids to membrane, 350 μL PBS in receiver, 100 μL PBS in donor
  - 100 μM drugs added to donor side
  - 1 plate inside altitude chamber, 1 plate outside chamber
  - 100 μL collected from donor ("blood") & receiver ("brain") sides
- LC-MS/MS Methods
  - UPLC-MS/MS by triple quadrupole Thermo Vantage
  - BEHC18 column (Waters), 10 min gradient, 0.1% formic acid/MeOH
  - Two transitions per drug
  - Calibration against internal $^{13}C_3$-caffeine standard in MeOH

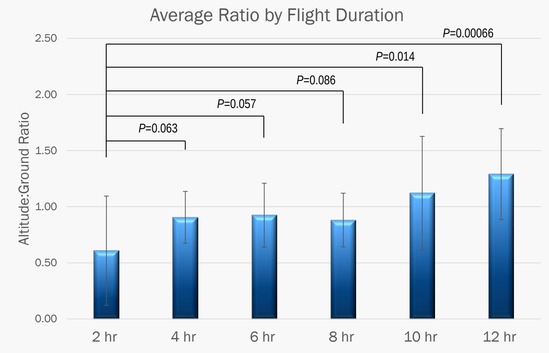


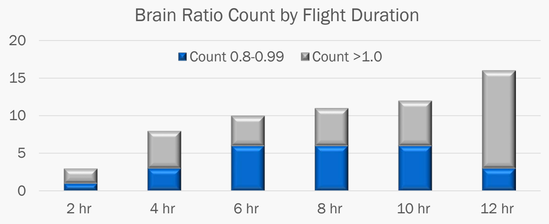
- Flight Simulations
  - USAFSAM training altitude chambers (Wright-Patterson AFB)
  - Simulated AE flight cabin pressurization climb/descent rate
  - Applied Standard Military Cabin Altitude (SMCA)
  - Simulated wheels-up to wheels-down AE flights CONUS/OCONUS

  See figure above for 2-h simulation

RESULTS







DISCUSSION

- No strong correlation or covariance between Lipinski's rule of five or Veber's drug likeness parameters and permeability changes
- Average altitude-to-ground brain-side ratios of 14 drugs were significantly increased toward altitude after 10 h
- Number of drugs with higher concentrations in the brain at 8,000 ft (altitude-to-ground ratio >1.0) increased with flight duration
- Number of drugs with transitive altitude-to-ground ratios (between 0.8 and 0.99) peaked between 6 and 8 h
- Total number of drugs with altitude-to-ground ratios above 0.8 increased with duration
- No apparent time-dependence for any drugs tested
- On-going analysis efforts
  - *In vitro* data for another 18 drugs
  - *In vitro* data for an *in vivo* imaging tracer
  - *In vitro* data obtained alongside *in vivo* experiment
- Efforts pending funding
  - PBPK/QSPR model for dose/cabin altitude
  - Active efflux from brain side

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The views expressed are those of the authors and do not necessarily reflect the official policy or position of the Air Force, the Department of Defense, or the U.S. Government.

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