Novel Perioperative Therapies

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Disclosures

Vanderbilt University has filed for patents and licensed citrulline as a therapeutic agent with Asklepion Pharmaceuticals

Dr. Barr has grant funding from both the NIH and industry sponsors (Asklepion Pharmaceuticals) for the study of intravenous citrulline

Perioperative therapies for Postop PHTN

- Inhaled NO (? Novel)
- Intravenous arginine
- Intravenous and oral sildenafil
- Inhaled iloprost & epoprostenol
- Intravenous and oral citrulline

Inhaled NO

- iNO is the only selective pulmonary vasodilator approved by the FDA for a neonatal indication (respiratory failure in term neonates)
- iNO has been studied and used extensively off label therapeutically in the postoperative setting
Randomized Clinical Trials of iNO

- Russel et al, Anesth Analg, 1998 (UCSF)
- 39 pts randomized to iNO at 80 ppm vs placebo for 20 minutes
- iNO significantly reduced mean PAP in patients with postop PHTN
- Morris et al, Crit Care Med, 2000 (Toronto)
- 12 children with postop PHTN, randomized sequential study
- iNO at 40 ppm plus hyperventilation reduced mean PAP in children with postop PHTN

iNO Clinical Trial Meta-Analysis

- Cochrane database review (Bizzarro and Gross, 2008) (Yale)
- Total of 162 patients
- No difference in mortality, number of PHT crises, physiologic outcomes between iNO and placebo groups
- Limitations of meta-analysis addressed including small sample size, methodology
- Larger RCTs need to address important outcomes
Intravenous Arginine Clinical Trial

- Many studies have evaluated effect of surgery on arginine levels
- Schulze Nieck et al (Circ, 1999) (London) evaluated effect of arginine and other therapies on postop PVRI
- Stepwise addition of FiO2 0.65, L-arginine (15 mg/kg/min), inhaled NO at 20 ppm in 10 children
- Significant effect of oxygen, arginine but not iNO

Intravenous Sildenafil

- Sildenafil increases intracellular cyclic GMP by inhibiting breakdown by phosphodiesterase-5 isoenzyme
- Stocker et al (Victoria, Australia) studied effects of IV sildenafil (0.35 mg/kg over 20 minutes) and inhaled NO (20 ppm) in 15 infants with postop PHTN after VSD or AVSD repair (Intens Care Med, 2003)
- Randomized sequential study- inhaled NO then IV sildenafil vs IV sildenafil then inhaled NO
Oral Sildenafil

- Raja et al (Glasgow) evaluated escalating doses of oral sildenafil on PA pressure in 10 infants with postop PHTN after VSD and AVSD repair (J Cardiothorac and Vasc Anesth, 2007)
- Doses used = 0.5 mg/kg up to 2 mg/kg q 4 hrs until extubation (also on inhaled NO)
- Sildenafil significantly lowered PA pressure without significant effects on systemic pressure or oxygenation
- Found that 0.5 mg/kg was just as effect as higher doses

Inhaled Iloprost (Ventavis)

- Inhaled prostacyclin (PGI2) has been suggested as an alternative to inhaled NO in the setting of postop PHTN
- Iloprost is a stable prostacyclin analog
- Limsuwan et al (Bangkok) studied nebulized iloprost (0.5 ug/kg- 2 ug/kg) delivered over 10 min q 30 min x 5 treatments) in 8 infants with postoperative PHTC (Int J Cardiol, 2008)
- Inhaled iloprost significantly reduced mean PAP from 47 to 30 mmHg and improved oxygen saturation without systemic effects

Inhaled iloprost and inhaled NO

- Rimensberger et al (Geneva) evaluated inhaled NO (20 ppm x 10 min), inhaled iloprost (0.25 ug/kg over 10 min), and combined inhaled NO and iloprost in sequential fashion in 5 infants with PHTN immediately after repair of VSD or AVSD lesions (Circulation, 2001)
- Inhaled iNO and inhaled prostacyclin had similar effects with a significant reduction in pulmonary vascular resistance
- The combination of inhaled NO and inhaled prostacyclin did not further decrease PVR

Inhaled epoprostenol (Flolan)

- Also a PGI2 analog used in IV form for management of primary pulmonary hypertension
- Can nebulize IV formulation in ventilated patients using miniHeart nebulizer
- Developed nebulized epoprostenol protocol at Vanderbilt Children’s to reduce or replace use of iNO
- Utilizes mini-Heart nebulizer inserted in ventilator circuit at flow rates of 2 l/min
Inhaled epoprostenol (Flolan)

- Case series of 10 postop patients on inhaled NO who were then transitioned to inhaled epoprostenol at a starting dose of 50 ng/kg/min.
- Eight of 10 patients successfully transitioned off iNO to inhaled epoprostenol with a reduction in oxygen index from 19.3 to 9.3 (p<0.05)
- Two patients had increase in OI after transition to epoprostenol and switched back to iNO
- One patient with poor response to iNO had good response to inhaled epoprostenol

Citrulline clinical studies

- Rationale for using citrulline
- Observational study of plasma citrulline levels
- Clinical trial with oral citrulline
- Safety and pharmacokinetic study with intravenous citrulline
- Status of intravenous citrulline efficacy trial
Why Citrulline and Not Arginine as a Precursor for NO synthesis

- Extracellular Reasons
  - Citrulline is not rapidly degraded by arginases ubiquitously scattered in all tissues.
  - Citrulline is not captured for protein/peptide production.
  - Citrulline is not captured by gut bacteria in enterohepatic circulation as a protein substrate or nitrogen source.

- Intracellular Reasons
  - Microgeography and substrate pools

Citrulline, arginine and NO production:
- Citrulline is transported by a neutral amino acid transport (SN1 likely) system
- The enzymes ASS, ASL, NOS are found physically bound together in the caveolar membrane

Citrulline levels after Cardiac Surgery

Oral Citrulline Trial after Cardiac Surgery
- Randomized double blind placebo control trial with 20 patients treated with oral citrulline and 20 patients with placebo. PHTN defined > 20 mmHg (Smith, JTCVS, 2007)
- Dosing based on citrulline replacement for urea cycle defect patients 4 gm/m². Target was 37umol/l
- Treatment began at surgery and continued for 48 hours.
Intravenous Citrulline Safety and PK study

- Determined that optimal bolus dose was 150 mg/kg to achieve a 4 hour trough of 100 umol/L
- Short ½ life of about 2 hours= continuous postop infusion
- Final protocol: Initial bolus of 150 mg/kg on CPB followed 4 hours later by continuous infusion at 9 mg/kg/hr yielded sustained plasma citrulline levels of 100 umol/L for 48 hours

Intravenous Citrulline PK study: In 26 patients only 2 with PHTN both with Down Syndrome (Barr, JTCVS, 2008)

Intravenous Citrulline Safety and PK study

FDA Meeting Dec 2007

- Discussion of study design and Outcomes
- Primary Outcome- Length of postoperative mechanical ventilation
- Secondary Outcomes:
  - Postoperative pulmonary hypertension
  - Length of Intensive Care Unit Stay
  - Length of chest tube drainage
  - Length of hospitalization
  - Utilization of inhaled nitric oxide
  - Mortality

Design

- Randomized Clinical Trial: 405 patients undergoing 1 of 5 surgeries (AVSD, VSD, Glenn, Fontan, Arterial switch)
- Randomized to IV citrulline (Citrupress) vs placebo protocol
- Randomization stratified by surgical procedure and site
- Patients will otherwise receive standard of care at the discretion of the treating clinicians
Study Status

- Enrolled 77 patients at Vanderbilt in a pilot study using a in house source of IV citrulline- data analysis just started
- Ready to start enrollment (May 2009) using the Citrupress formulation at several other centers

Citrulline Multicenter Study Sites

Anticipated study completion by end of 2010
CRO- Pharmalink, Inc
- **US Sites:**
  - Vanderbilt Children’s (Rick Barr)- coordinating center
  - St. Louis Children’s (Allan Doctor)
  - Cincinnati Children’s (Catherine Dent)
  - Riley Children’s, Indianapolis (Chris Bysani)
  - Chicago Hope Advocate Heart Institute for Children (Andrew Van Bergen)
  - Denver Children’s (Dunbar Ivy)
  - Chicago Children’s Memorial-Northwestern (Ranna Rozenfeld)
- **International Sites:**
  - Birmingham Children’s (Birmingham, UK)
  - Sirraj Hospital (Bangkok)
  - Ramathibodi Hospital (Bangkok)
  - Chulalongkorn University Hospital (Bangkok)

Summary: Novel Perioperative Therapies

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