DATA AND SAFETY MONITORING PLAN: Data reviewed 10/04

Title: Precursor Preference in Surfactant Synthesis of Human Preterm Infants
HSC# 02-0898

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1. Detailed description of data and safety monitoring plan

Each patient enrolled will be reviewed by the PI to ensure eligibility, that all required studies are obtained, and that any adverse events are identified immediately.

a. General data to be reviewed:
   i) Certification of purity, sterility, and pyrogenicity of isotope preparations: attached
   ii) Number of subjects approached and number consented
   iii) Eligibility of subjects infused
   iv) Number of subjects for whom the study was not completed and reasons
   v) Number of subjects who withdrew from the study and reasons
   vi) Number of subjects who developed electrolyte disturbances (acid-base balance, hypernatremia) during the isotope infusion

b. Specific data to be reviewed (individual case review and overall numbers):
   i) Subjects who die within 1 month of the study
   ii) Subjects who develop bloodstream infections within 1 month of the study

c. Review of specific unanticipated adverse events
   If an unanticipated adverse event occurs, the PI will convene an ad hoc meeting of a group to review the specifics of the event.

The data will be reviewed every three months. The Human Studies Committee will be notified in writing within 15 days of any adverse events that may be reasonably be regarded as being caused by, or probably caused by, the study protocol. Furthermore, if other complications, such as infection, electrolyte imbalance, etc, occur in excess of the rate in a comparable population of infants, the study will be stopped, and the Human Studies committee notified. Adverse events that might be anticipated will be reported if they are life threatening or result in death.

<u>Statistics</u>

Eight patients $\leq$ 28 weeks estimated gestational age were selected at random from our list of patients approached, but not infused. These 8 preterm infants were used as controls for evaluation of current rates of infection and electrolyte disturbances in their first 2-4 weeks of life.

Subjects Approached: 44

Subjects Consented: 25

Subjects Infused: 18 (7 patients withdrawn by PI or attending prior to infusion secondary to clinical status or extubation)

Subjects with bacteremia one month post-infusion: 2 (both with central lines present). Out of the 8 controls, 5/8 had positive blood cultures.

Subjects with development of hypernatremia (N> 145) during infusion: 2. Hypernatremia is very common in the first week of life in extremely premature infants. Of the 8 control infants 4 had sodium levels greater than 145.

Subjects with hypernatremia less than one week after the infusion: 3. See above explanation.

Subjects with development of alkalosis (pH> 7.5) during infusion: 1. It is not uncommon for infants to develop a respiratory alkalosis as this patient did from a more aggressive ventilation strategy. The alkalosis was a result of a low carbon dioxide level not a high bicarbonate level. A high bicarbonate level is more consistent with a side-effect from our study infusion which includes acetate. 3/8 of the control patients developed a pH >7.5 in the first 2-4 weeks of life.

Subjects with development of alkalosis (pH> 7.5) during one week after the infusion: 3. See above explanation.

Subjects with development of hypercarbia (pCO_2 >60) during infusion: 7. Hypercarbia is extremely common in preterm infants. All of the control infants had hypercarbia at some point in the first 2 weeks of life and many had multiple episodes of hypercarbia.

Subjects that died less than 1 month after the infusion: 1. This patient died approximately 16 days after the infusion. Her death was secondary to pulmonary hypoplasia and hypertension. Upon further review by the attending physician and principal investigator, the child's death was unrelated to participation in the study. Of the 8 control patients 2 died.