Development of Thyroid Hormone as a Treatment Therapy for Acute Respiratory Distress Syndrome

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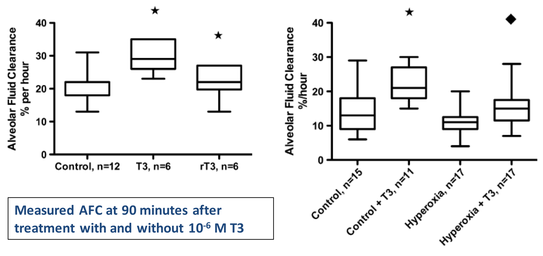
Introduction and Background

- Acute respiratory distress syndrome (ARDS) is characterized by proteinaceous pulmonary edema, inflammation and hypoxemia with a mortality rate of 40% and no proven molecular therapies.
- The edema in ARDS results from increased epithelial permeability and reduced alveolar fluid clearance (AFC).
- AFC occurs by active sodium transport with coordinated action of epithelial sodium channels and the sodium pump, Na^+-K^+ ATPase.
- Thyroid hormone (T3) has multiple effects on type-II alveolar epithelial (AT2) cells, including increased AT2 Na^+-K^+ ATPase pump activity.
- Intraperitoneal or intratracheal T3 instillation increases AFC i*n vivo* in both normal and hyperoxia-injured rat lungs (*Bhargava 2008).*
- T3 decreases lung fibrosis in animal models of lung fibrosis *(Yu 2018).*
- Postmortem lung tissue of ARDS patients has very low lung tissue T3.
- T3 has never been tested in ARDS patients or via direct airway instillation.
- We planned a phase I/II clinical trial to assess the safety and efficacy of T3 to increase AFC and reduce extra-vascular lung water (EVLW) in ARDS patients.
- To provide safety data to support our investigational new drug (IND) application for this novel intratracheal (i.t.) route of administration in human subjects, the safety of intratracheal T3 was assessed in a rat GLP toxicology study *(Flory 2021)*.

Airspace instillation of T3 into *ex vivo* rat lungs rapidly increases AFC in normal & hyperoxia-injured lungs



Measured AFC at 90 minutes after treatment with and without 10^{-6} M T3

In vivo

- T3 rapidly increased the AFC compared with controls ($P < 0.05$).
- rT3 did not alter the rate of fluid resorption ($P = 0.47$).

Ex Vivo

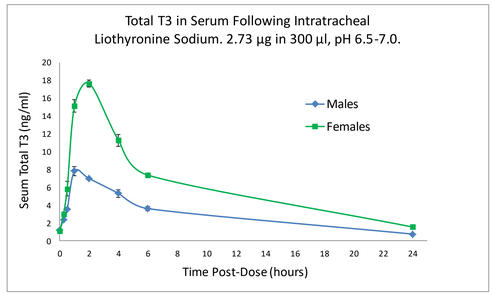
- T3 increased AFC by 61.5% compared to control intact lungs ($P < 0.05$)
- In hyperoxia-exposed rat lungs, T3 instillation increased AFC within 90 minutes ($P < 0.05$).

Design of IND-enabling preclinical safety study

- Goals: Assess the safety and pharmacokinetics of an intratracheal route of T3 administration.
- After transient anesthesia and intubation, study drug was instilled directly into the rat trachea once per day for 5 consecutive days.
- T3 was administered at the maximum feasible dose (MFD) for repeat administration, ~2.7 µg in 300 µl.
- Study was conducted in compliance with Good Laboratory Practices (GLPs).

	Toxicity Phase		Toxicokinetic Phase	
Group	Number of Main Animals		Number of Toxicokinetic Animals	
	M	F	M	F
Liothyronine Sodium Vehicle (Control)	10 + 2	10 + 2	0	0
Normal Saline (Control)	10 + 2	10 + 2	0	0
Liothyronine Sodium Injection	10 + 2	10 + 2	12	12
Totals	30 + 6	30 + 6	12	12
	60 + 12		24	
	96			
Dosing Frequency & Duration	Dosed daily for 5 days		Single Dose	
Scheduled Termination	1 Day post final dose		Day 1	
TK Blood Collection	NA		At designated time point	
Clinical Pathology and Histology	Yes		NA	

Total T3 in serum following intratracheal delivery of 2.7 µg of T3

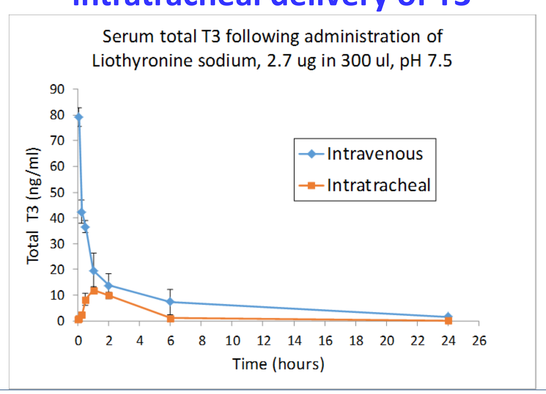


Toxicokinetic parameters following intratracheal delivery of 2.7 µg of T3

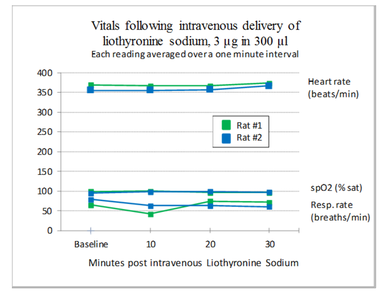
Sex	Cmax (ng/mL)	Cmax_D (ng/mL/ug)	Tmax (hr)	HL_Lambda_z (hr)	AUClast (hr*ng/mL)
F	16.53	6.12	2.00	2.85	64.08
M	6.60	2.44	1.00	3.17	25.38

Sex	AUCINF_obs (hr*ng/mL)	AUCINF_D_obs (hr*ng/mL/ug)	Cl_F_obs (mL/hr)	Vz_F_obs (mL)
F	89.70	33.22	30.10	123.60
M	36.34	13.46	74.29	339.44

Comparison of total T3 in serum following intravenous or intratracheal delivery of T3



Vital signs following i.v. delivery of T3



There were no acute effects on any of the physiologic parameters measured following either i.v. delivery of 2.7 µg T3 or following five days of intratracheal administration (data not shown).

Preclinical Safety Study Summary

Intratracheal T3 administered on 5 consecutive days to intubated rats at a MFD, showed:

- No adverse clinical findings
- No drug related safety findings – clinical laboratory and histopathologic endpoints.

This no-effect dose is approximately 30-fold greater than the highest projected clinical dose.

Phase I/II Ongoing Clinical Trial

Objectives: Determine the safety, tolerability and effects on EVLW of i.t. T3 delivery into the lungs of ARDS patients.

Primary Endpoint: Composite of drug-related serious adverse events (esp pulmonary/cardiac)

Study Population: 68 patients (50 treatment, 18 control) with a clinical diagnosis of ARDS.

Study Centers: Essentia Health-St. Mary's Medical Center (Duluth, MN); University of Minnesota Medical Center (Minneapolis, MN).

Results: Phase I completed, Phase II enrolling.

- No instillation-related adverse events.
- No treatment-related SAE's, abnormal safety labs, vitals signs or elevated systemic T3 conc.