TREHALOSE STABILIZED FREEZE DRIED HUMAN PLATELETS, THROMBOSOMES®, PERSIST IN CIRCULATION 24 HOURS AFTER INFUSION AND ARE NON-IMMUNOGENIC IN NEW ZEALAND WHITE RABBITS

Vibhudutta Awasthi*, Josh Dee, Mike Fitzpatrick, Anna Koh, Richard Cliff, Giora Feuerstein

*Cellphire, Inc. Rockville, MD; *University of Texas Health Center at San Antonio*

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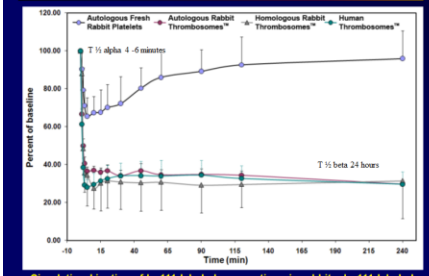
ABSTRACT

Thrombosomes®, a human platelet derived hemostatic agent, (PDHA) is being developed to meet a critical unmet medical need, e.g. a safe PDHA that restores hemostasis in patients with a coagulopathy that does not respond to standard treatment. Submission to regulatory agencies for approval requires analyzing the pharmacokinetics of this PDHA including the circulation characteristics in comparison to stored platelets (3 days old) and determining their safety and immunogenicity.

MATERIALS AND METHODS

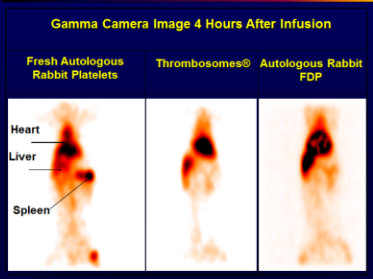
- Thrombosomes® is produced by a proprietary process that includes trehalose and other carbohydrates and a custom lyophilization cycle.
- The PK, Biodistribution studies involved the infusion of In-111-labeled fresh rabbit platelets, human stored platelets (3 days old), human Thrombosomes®, and autologous or allogeneic rabbit freeze dried platelets (FDP).
- Anesthetized animals were infused with 2 x 10^9 (1mL) In-111-labeled cells over a one minute period.
- The radioactivity in serial arterial blood samples (100 µl) obtained over 4 or 24 hrs was assessed using a gamma counter.
- Potential impact of repeat dosing of Thrombosomes® on future repeated exposures (possibly immune mediated) has been studied by an infusion of Indium-111 labeled Thrombosomes 14 days after a single non-labeled infusion of the same dose.
- The effect of 3 intradermal exposures to Thrombosomes® (day 0, 14, and 21) on the PK and biodistribution of a single IV infusion of labeled Thrombosomes between 56 and 82 days after sensitization was no different from the effect of sensitization with a single IV infusion (data not shown)
- The biodistribution of the labeled cells was determined by imaging animals with a Gamma camera and determining the percent of injected label per organ and as counts per gram/organ at necropsy.

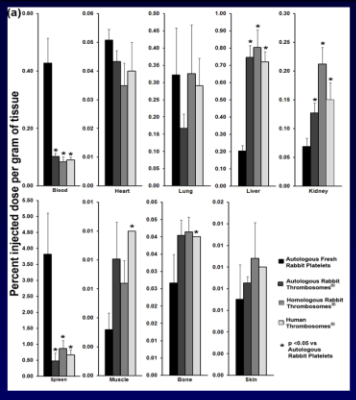
PHARMOCOKINETIC STUDIES



Circulation kinetics of In-111-labeled preparations in rabbits. In-111-labeled fresh autologous platelets served as a control for comparison. All radioactive counts were normalized to the baseline counts measured in the blood sample that was obtained immediately after infusion was complete.

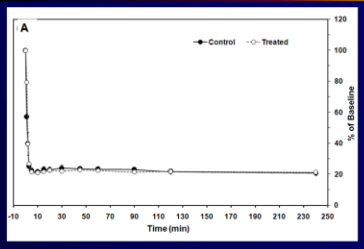
BIODISTRIBUTION

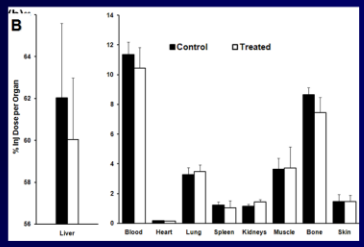




Accumulation of In-111-labeled fresh autologous platelets and various freeze-dried preparations in rabbits. The values are expressed as mean ±sem % injected dose (ID) per gram of tissue (N=4 per group). For convenience, the data for each organ have been separately plotted on different Y-axis scales. *p<0.05.

REPEAT EXPOSURE PK/BIODISTRIBUTION STUDIES





Biodistribution and PK of a second dose of In-111-labeled Thrombosomes® in rabbits that had been exposed to intravenous Thrombosomes®. The first and the second dose were separated by 14 days. Each data point is an average (± sem) of at least four samples. (A) Data represented on per gram tissue basis, (B) circulation kinetics of the In-111-labeled second dose.

CONCLUSIONS

- A large percentage of Thrombosomes® or rabbit FDP 60% to 70% are rapidly removed from circulation. The remaining 30% to 40% demonstrate a half life of about 24 hrs.
- The biodistribution and circulation data suggest that the origin of platelets used for Thrombosomes® generation does not affect their circulation persistence, but the freeze drying process significantly increases the clearance of platelets from circulation and uptake in liver, kidney and spleen.
- Safety studies in NZWR and beagles at 70 times the dose administered during the PK and biodistribution experiments failed to observe any test article associated AE or SAE including histopathological changes in the liver, kidney and spleen. POSTER P-0454