Dodecafluoropentane Emulsion in Acute Ischemic Stroke, a Phase 1b/2 Randomized and Controlled Trial

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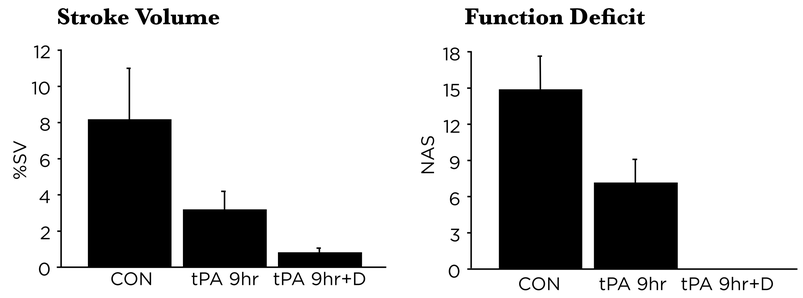
Phase 1b/2 Trial

Introduction

In Acute Ischemic Stroke (AIS) the effective therapeutic window remains very short for the vast majority of patients and severely limits those who qualify for acute therapy. The oxygen transporting nanodroplet Dodecafluoropentane Emulsion (DDFPe) (NuvOx Pharma, Tucson, AZ) given IV within 3h of onset can reduce AIS symptoms and stroke volumes markedly in animal studies and may widen the window significantly for therapy. Fig 1.

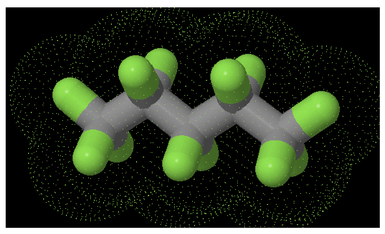
Fig. 1 Successful Rabbit Delayed Reperfusion with DDFPe

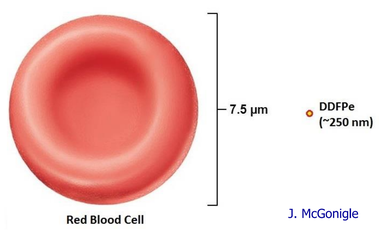


N= 24. Control=6, tPA=11, tPA+DDFPe=7

%SV: DDFPe, mean 0.80 vs tPA alone, mean 2.24, p=0.0018. Control vs tPA alone=NS. Kruskal Wallis + Bonferroni

NAS values: DDFPe, mean 0, is better than tPA alone p=0.0052, tPA vs controls p=0.029, NS Kruskal Wallis + Bonferroni requires <0.025





We conducted a randomized, placebo-controlled, double-blinded dose escalation AIS trial to demonstrate the Maximum Tolerated Dose, characterize adverse events, and explore impacts on acute NIHSS values and long-term outcomes. Doses of 0.05, 0.10, and 0.17ml/kg were based on successful rabbit data scaled to humans using surface area/weight formula.

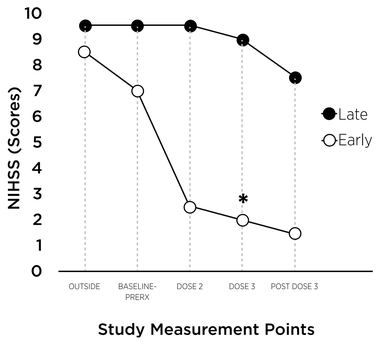
Methods

AIS patients with NIHSS of 2-20 were randomized to either 3 doses of IV DDFPe or placebo, one every 90 minutes, starting within 12 hours of symptom onset. Doses were given as soon as possible between unmodified standard stroke care elements. Each dose cohort included 8 patients, with 2 receiving placebo and 6 DDFPe. Primary outcomes were SAEs, AEs, NIHSS values, and mRS.

Results

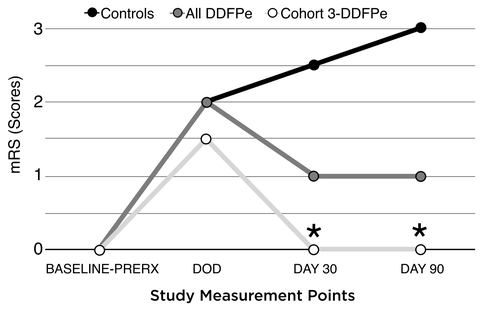
No Dose Limiting Toxicities were encountered and no maximum dose defined. One unrelated delayed death occurred in the DDFPe group and one in the placebo group. SAEs and AEs were of similar incidence in test and control groups and did not increase with dose. None were related to the drug. Headache, hypertension and cough, 5 of 24, were most common. Exploratory aims show early DDFPe treatment had better NIHSS values at 4.5h than late doses, p=0.03. Fig 2. In high dose DDFPe cohort mRS outcomes suggested improvement p=0.01 at 30 days and p=0.03 at 90 days. Fig 3, 4.

Fig. 2 Early DDFPe vs Late DDFPe, NIHSS



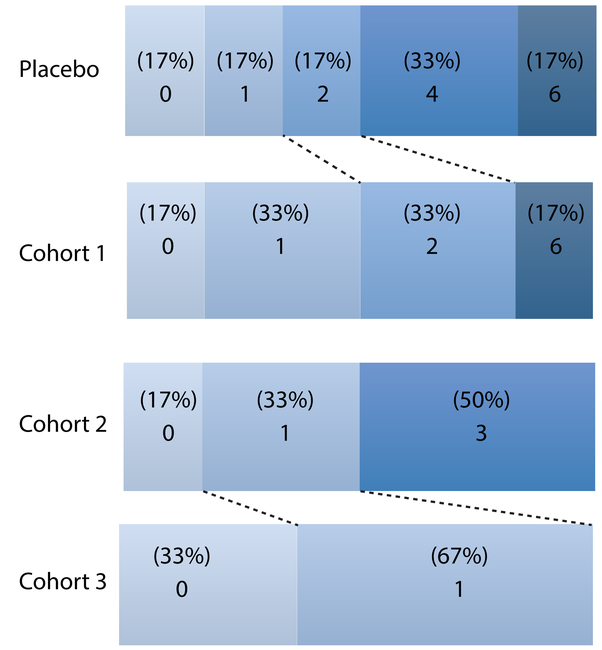
Early, <5 hr since onset N = 4
Late, >9 hr since onset N = 4

Fig. 3 Clinical Outcomes, mRS



Total N = 24
Controls = 6
DDFPe = 6 per cohort
* P = < 0.03

Fig. 4 Clinical Outcomes, 90 day mRS



Conclusion

IV DDFPe appeared safe at all tested doses. No MTD was defined. Exploratory Aims suggest that early DDFPe treatment improves NIHSS quickly and high dose DDFPe patients suggested improved outcomes. Larger trials are warranted.

References

1. Culp WC, Woods SD, Skinner RD, Brown AT, Lowery JD, Johnson JLH, Unger EC, et al (2012) Dodecafluoropentane emulsion decreases infarct volume in a rabbit ischemic stroke model. J Vasc Interv Radiol 23:116-121. DOI 10.106/j.jvir.2011.10.001
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Disclaimer

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