ON-DEMAND PULSATILE INTRACEREBRAL DELIVERY OF CARISBAMATE CONCURRENT WITH CLOSED-LOOP DIRECT NEUROSTIMULATION THERAPY IN A SELF-SUSTAINED LIMBIC STATUS EPILEPTICUS (SSLSE) RAT MODEL

3.064

AES 2010

Erwin Z. Mangubat* MD,MPH, Marvin A. Rossi MD,PhD,

Departments of Neurosurgery & Neurological Sciences, Rush Epilepsy Center

Rush University Medical Center (RUMC), Chicago, IL 60612 USA

1. SPECIFIC AIM

The goal of this work is to establish the preclinical feasibility of ameliorating spontaneously re-curring limbic seizures using closed-loop direct neurostimulation therapy in tandem with on-demand pulsatile intracerebral delivery of the novel antiepileptic drug carisbamate (Johnson & Johnson Pharma-ceutical Research & Development).

2. METHODS

A. Subjects:

Twenty F344 male rats (300-330 gms), 5 subjects/condition group (**Figure 1**), were used. Preliminary analyses are available for 11 subjects.

B. Methods:

1. During pentobarbitol anesthesia, stereotactic coordinates were used to guide a customized 16-contact dual fluidic-recording microelectrode shaft (NeuroNexus Tech.) into the right dorsal dentate gyrus (DG) of the hippocampal formation (HF), and a 16-contact non-fluidic microelectrode shaft into the left DG (**Figure 2A**). A stainless steel Teflon-coated twisted bipolar stimulating electrode was stereotactically placed in the medial division of the right perforant path (PP), 8mm posterior to bregma. Evoked potentials were used to confirm placement of all electrodes (**Figure 2B**).

2. Following a 6-day post-implant recovery period, a 1-hr pre-SSLSE baseline electrocorticogram (ecog) was acquired. Each freely moving animal then underwent a 90-min electrically-induced SSLSE protocol, inducing spontaneous limbic seizures. A line length signal processing algorithm (DataWave Technologies) was used to detect electrographic ictal onset patterns recorded from the distal eight serially arranged contacts in the HF. Successful detection automatically triggered stimulation therapy parameters (50uA less than the afterdischarge current, 1ms pulse duration, 100msec burst duration at 50 Hz, **Figure 3**).

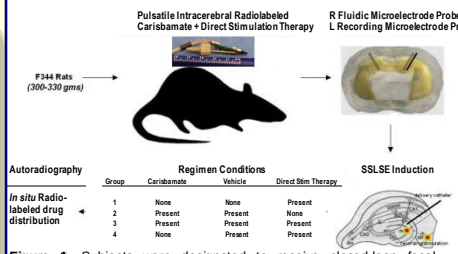

Figure 1. Subjects were designated to receive closed-loop focal stimulation therapy delivered to the right PP as outlined in the above regimen conditions. Stimulation therapy was delivered in the absence (Group 1 & 4) or presence (Group 2 & 3) of on-demand 20nl boluses of 0.10mg/50ul [14C]-carisbamate. The carisbamate was bolused at a rate=500nl/min. The drug was always delivered in the right DG.

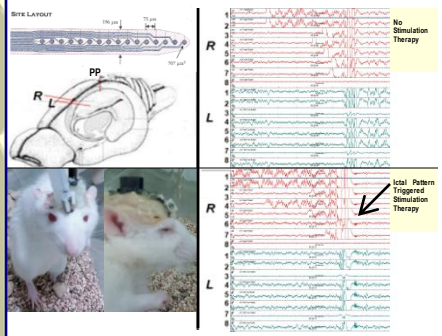

Figure 3. Ecog example of HF seizure termination associated with closed-loop stimulation therapy delivered to the right PP. The semi-chronic PP stimulating electrode was placed 7mm posterior to the right dorsal HF depth recording microelectrode array.

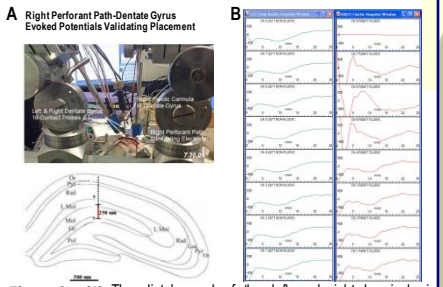

Figure 2. **(A)** The distal end of the left and right hemispheric microelectrode probe shafts targeted the middle molecular layer of the DG bilaterally. **(B)** Placement was confirmed by extracellular evoked potentials. Stimulation was delivered through the PP electrode.

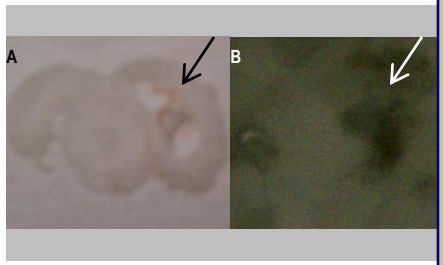

Figure 4. Each animal was sacrificed and brain tissue immediately frozen on dry ice in M1-embedding matrix after an 8 hour therapy session. [14C]-sensitive film was exposed to 10um tissue sections **(A)** for 42 days at 4°C prior to developing to demonstrate radiolabeled drug distribution **(B), see arrows**.

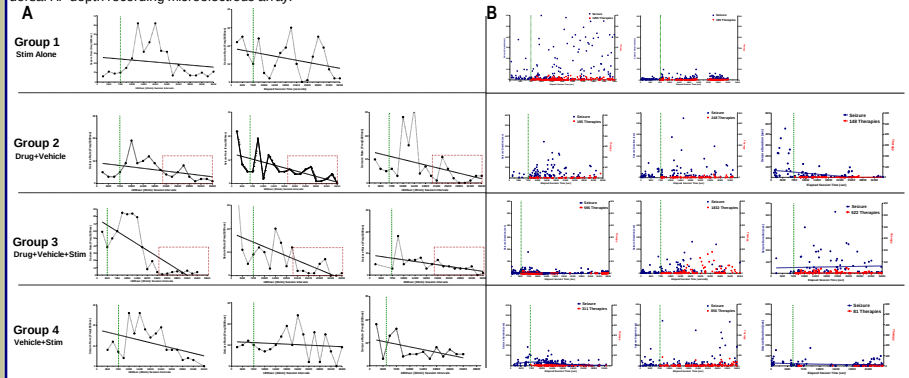

Figure 5. Electrographic seizure frequency/30min intervals **(A),** and seizure duration **(B)** were assessed over an 8hr (28800sec) recording/therapy delivery session, following a 2hr (7200sec) post-SSLSE/pre-therapy baseline interval (green dashed line). Red boxes **(A)** indicate stabilization of decreased seizure freq in groups 2 & 3. The data were tabulated by a blinded evaluator (MAR) reviewing the entirety of each ecog session with video.

3. RESULTS

Closed-loop stimulation therapy delivered axonally along the perforant path is shown to abort electrographic seizure activity detected in the HF of the SSLSE animal model (**Figure 3**).

Autoradiography demonstrates targeted ipsilateral HF distribution of nano-bolused positive-pressure delivery of [14C]-carisbamate concentrations from the distal shaft of the hybrid recording depth microelectrode shaft (**Figure 4**).

Overall, efficacy was measured with linear regression analysis using the frequency of electrographic seizures occurring per 30 minutes (1800sec) over the 8hr (28800sec) recording-therapy session (**Figure 5A**).

Delivery of on-demand focal stimulation therapy alone (group 1), or with vehicle (group 4), demonstrated marked variability.

In contrast, delivery of nano-bolused carisbamate in the absence (group 2) or presence (group 3) of stimulation therapy revealed a low seizure frequency with minimal variability (**Figure 5A dashed red boxes**) compared to groups 1 & 4.

Electrographic seizure duration did not demonstrate a consistent pattern throughout the post-SSLSE 8hr recording-therapy session. In addition, ictal duration was independent of total therapy boluses delivered (**Figure 5B**).

4. CONCLUSIONS

Preliminarily, direct neuro-stimulation therapy delivered in the ipsilateral pathological PP can stabilize an epileptic circuit where the ictal onset is detected at a distance in either the ipsi- or contralateral DG. In addition, a trend is seen toward a decreased frequency of electrocerebral seizures in those subjects receiving closed-loop direct neurostimulation therapy in tandem with on-demand intracerebral low concentration carisbamate therapy, compared to closed-loop stimulation therapy alone (group 1), or with vehicle only (group 4).

In addition, [14C]carisbamate delivery isolated to the HF underlines the ability of targeted nano-bolused drug delivery to spare exposure of normal brain regions to drug.

Such a strategy can simplify the surgical approach while maximizing efficacy with the available intracranial electrode set.

On-demand delivery of nano-bolused intracerebral anti-epileptic molecules is a promising strategy for augmenting closed-loop direct stimulation therapy in refractory localization-related epilepsy

FUNDING SOURCES

1. Ortho-McNeil Janssen, LLC
2. Institutional (RUMC)