1. SPECIFIC AIM

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

2. METHODS

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

B. Methods:

1. During pentobarbital anesthesia, stereotactic coordinates were used to guide a customized 16-contact dual fluid-recording microelectrode shaft (NeuroNexx 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 parietal cortex (PP), 3mm posterior to bregma. Evoked potentials were used to confirm placement of all electrodes (Figure 2B).

2. Following a 24-hr post-implant recovery period, a 1-hr pre-SSLSE baseline electrocorotigram (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 electrophysiological idioseizure patterns recorded from the distal eight serially arranged contacts in the HF. Selective detection automatically triggered stimulation therapy parameters (50uA less than the afterdischarge current, 1ms pulse duration, 100msec burst duration at 50 Hz, Figure 3).

3. RESULTS

Closed-loop stimulation therapy delivered axonally along the perforant path is shown to abate 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 (1800/sec) over the 8hr (2880/sec) recording-therapy session (Figure 5).

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

In contrast, delivery of nano-bolus 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).

3. CONCLUSIONS

Preliminarily, direct neurostimulation 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 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-bolus 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)