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Example - Early Feasibility Investigational Device Exemption

IDE Section:

Prior In Vivo Studies

5. Prior *In Vivo* Studies

This section contains:

5.1. Overview

Electrical stimulation of nerves is a commonly used technique for treatment of various diseases and disabilities. This section describes the past studies of the safety of electrical stimulation in the animal model, with a focus on the studies that have direct relevance to the NNP System. The key parameters that affect the safety of stimulation have been identified and the safe range of these parameters has been identified. There is now a long history regarding the use of electrical stimulation devices with electrodes implanted near, on, or in, nerves, providing ample evidence of the safe use of electrical stimulation. The specific electrical stimulation parameters utilized in the NNP System are compared to these data and shown to be within safe stimulation levels.

The summary presented here reviews animal studies; prior human studies are summarized in *4.0 Prior Clinical Studies*. The seminal safety studies, however, predominantly involve animal experiments in which direct tissue response was evaluated. **Based on these past findings, we conclude that no further *animal* studies are necessary to characterize the safety of the electrical stimulation parameters used in the NNP, or the electrodes themselves.** Please refer to the Device Evaluation Strategy Table (in *6.0 Device Evaluation*).

5.2. Summary Of *In Vivo* Safety Studies Of Electrical Stimulation

Safe stimulation of living tissue can be achieved by the proper selection of stimulus parameters and electrode design. The electrochemical reactions that occur near each electrode have been studied extensively. Although the exact mechanism by which stimulation can induce tissue damage is unknown, the critical parameters have been identified. The critical parameters include:

- Charge balance,
- Charge per phase,
- Charge density per phase,
- Electrode geometry, and
- Electrode material.

Studies in the 1970's comparing monophasic and biphasic stimulation demonstrated that tissue and electrode damage can be greatly reduced by utilizing a balanced-charge biphasic waveform [Mortimer, 1981]. In general, the first phase is cathodic (at the activating electrode) and is typically a rectangular pulse defined by the pulse duration (PD) and pulse amplitude. The second phase is anodic and can take various shapes, with the key factor being that the total anodic charge is equal in magnitude to the total cathodic charge. A brief (50-100μs) delay between the end of the cathodic phase and the beginning of the anodic phase improves the effectiveness of the pulse.

Charge per phase and charge density per phase of the cathodic activating pulse have been identified as primary factors in determining safe stimulus levels [Pudenz, et al., 1975; Mortimer, 1981; Agnew, et al., 1990a; McCreery, et al., 1990]. Figure 1 summarizes some of the safe stimulus levels established for these two parameters in different tissues. In general, charge densities in the range of 10-100 $\mu C/cm^2$ per phase are in the safe region for brain tissue, and even higher charge densities can be tolerated in the peripheral nervous system (see human studies below).

The tissue response is independent of stimulus frequency when the frequency is below 50Hz. Most motor neuroprosthetic applications, including the NNP System, use frequencies

of 20Hz or lower, so frequency is not a factor. For stimulation rates above 50Hz, there is some evidence of a "mass action" effect, in which damage occurs in the nerves due to the increased overall nerve activity [Agnew, et al., 1990b; McCreery, et al., 1992; McCreery, et al., 1995]. This has the effect of reducing the expected safe levels of charge density per phase when higher frequencies are used.

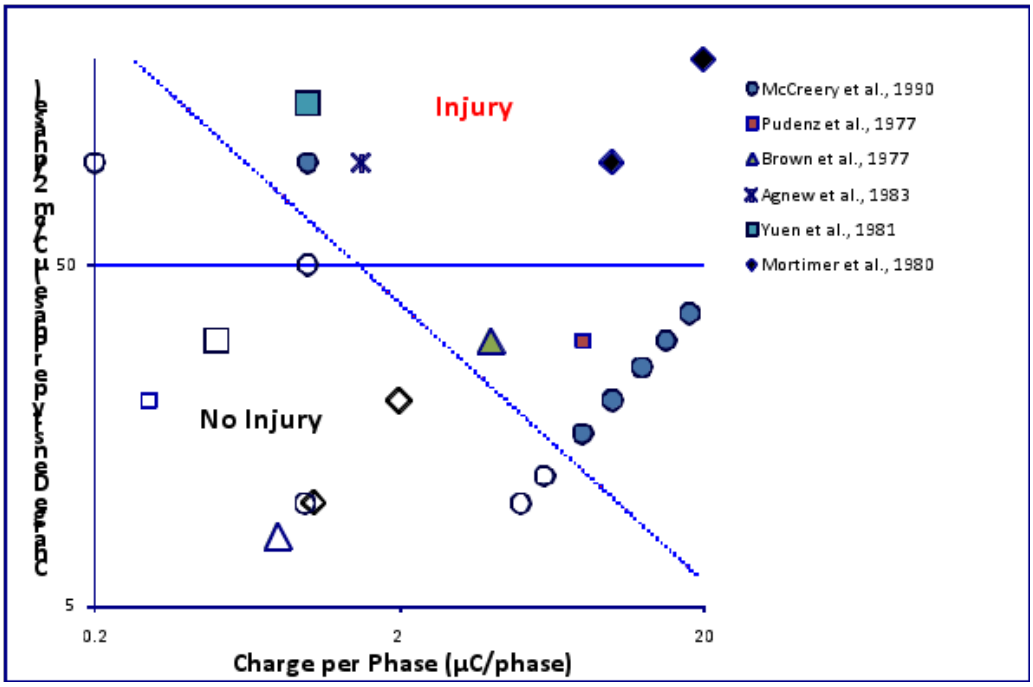

Figure 5-1. Summary of safe stimulation studies. Open symbols indicate parameters where no damage was identified and Closed symbols indicate parameters where damage was identified.

It should be noted that all studies of "damaging" stimulation are based on the expectation of continued chronic delivery of the stimulation at the damaging level. Thus, in terms of a dose-response characteristic, the "maximum" dose is always tested. However, this is not a realistic test condition for the situation in which a device *fails* in some manner and begins delivering imbalanced charge into the tissue. In these conditions, the muscle response will immediately change, possibly even accompanied by significant altered sensation in the limb, and the user will immediately turn the stimulation off, usually within a few seconds.

Recently, we and others have examined more realistic "fault" conditions in which the duration of imbalanced charge is brief [Ackermann, 2009]. We found that direct current at 1.4mA could be delivered for an average of 16 seconds before any reduction in the conduction of motor action potentials, and an average of 41.2 seconds before complete loss of motor conduction. Thus, there is a significant time window in which the user can identify a suddenly altered response and inactivate the stimulation without incurring even temporary nerve damage. This is particularly relevant to the NNP System because it does not have fault conditions that lead to *chronic* "over" stimulation. Thus, even in the case where a failure in an implanted device delivers direct current (itself an unlikely event), nerve damage is unlikely.

Finally, permanent disability due to peripheral nerve damage caused by electrical stimulation is extremely unlikely without *continued* chronic conditions. This is because peripheral nerves, unlike nerves in the central nervous system, have a high propensity for spontaneous recovery and regrowth. In fact, if a peripheral nerve is crushed or severed without physical separation of the nerve endings, neurological recovery is good [Reyes et al., 2005]. Acute nerve compression is treated conservatively, without surgical intervention, because of the high incidence of spontaneous improvement [Miller, 1984]. An example of this principle is the use of phenol neurolysis for treatment of pain or spasticity. These treatments must be repeated after 6-18 months because reinnervation has occurred [Halpern et al., 1967; Yadav et al., 1994]. The robust capacity of peripheral nerve to regenerate is very relevant to the NNP System. All components of the NNP System are located in the periphery, and all electrodes are located on or near peripheral nerves. This is in distinct contrast to many commercial pulse generators that deliver stimulation directly to the central nervous system, which does not regenerate (e.g. deep brain stimulators and spinal cord stimulators). Given this, it is extremely difficult for the NNP System to cause permanent injury through the action of electrical stimulation alone.

A variety of **safe and durable electrode materials** have been identified and utilized in pre-clinical and clinically deployed electrical stimulation devices. Common electrode materials are 316LVM stainless steel, platinum and platinum-iridium (90%-10% most commonly) [Smith et al., 1987; Naples et al., 1990]. Titanium is commonly used as the return current electrode, particularly when the pulse generator case serves as the return. Other materials have been evaluated due to their potential for increased charge density, such as tantalum and activated iridium, but these are of primary interest for use in intra-cortical activation, where the tissue is more sensitive and where very small surface areas are required. The effective surface area of an electrode can also be increased through surface treatments such as bead blasting or sintering.

Electrode geometry is primarily important for the direct mechanical affect of the electrode on the tissue rather than the electrochemical impact. Electrodes should not have sharp surfaces and should be anchored in the tissue to avoid abrasion effects during voluntary movement, and to minimize the chance of migration. Lead routing should be oriented so that the lead tethering does not place significant torques on the electrode. Leads should also be routed so that they do not lay next to a nerve, which may result in compression damage.

5.3. *In Vivo* Safety Study of Epimysial and Intramuscular Stimulating Electrodes

A pre-clinical study was conducted to assess the *in vivo* performance of the CWRU epimysial and intramuscular stimulating electrodes that will be utilized as part of the NNP System (see *2.0 Device Description* for a detailed description of these electrodes). Four dogs were each implanted with an implantable stimulator, four epimysial electrodes, and four surgically-implanted IM electrodes [Akers et al., 1996; Memberg et al., 1994]. The electrodes were implanted in pairs (one epimysial, one intramuscular) on/in four muscles of the dog's foreleg. Implant times ranged from 10 to 33 months. One electrode in each pair was chronically stimulated, using a paradigm modeled after the exercise stimulation patterns used by our human subjects, in order to evaluate the effects of electrical stimulation when using these electrodes. Stimulation was applied for 8 hrs/day, 5 days/week, for 8 weeks. The second electrode in each pair served as a control for the tissue response attributable to surgical, material, and mechanical factors. Once the 8 weeks of stimulation was completed, the devices remained implanted and passive for another five weeks to allow for resolution of any acute inflammatory response that may have occurred in response to the stimulation.

Histological studies revealed that the tissue response to the surgically-implanted IM electrode was well within acceptable limits and comparable to that observed with epimysial electrodes. There were no signs of infection or adverse response. Tissue responses were judged according to a six-level ordinal rating scale. Upon surgical retrieval, all implanted devices were found to be encapsulated in thin fibrous capsules with no sign of infection. Microscopic examination revealed that these capsules consisted primarily of collagen and fibrocytes, with occasional to numerous macrophages. For the surgically-implanted IM electrodes, immediately adjacent to the electrode's surface, there was a thin layer of fibrous tissue with fibroblasts and macrophages growing into the crevices between the wires of the stimulating surface. Between this layer and the muscle tissue was a predominantly inactive collagenous fibrous tissue layer. Cells that are the hallmarks of acute or chronic inflammatory responses (polymorphonuclear leukocytes, lymphocytes, plasma cells) were very rarely seen. The mean thickness of the thickest portion of the fibrous capsule around the surgically-implanted IM electrodes' stimulating region was 0.70 mm with a standard deviation of 0.51 mm. For neither electrode type was the fibrous response rating shown to be correlated with the presence of chronic stimulation or the level of stimulation ($\alpha = 0.05$). These results are consistent with the expected mild foreign body response that is well documented in the literature. The tissue response to all of the electrodes was judged to be clinically acceptable. Based on these positive results, both of these electrode designs have been utilized in CWRU implantable systems, including those covered under IDEs G890084, G900108, G950116 and G040214, as well as PMA P950035.

5.4. GLP Statement

All animals used for in-vivo studies were obtained through CWRU Animal Resource Center, which complies with all regulations governing the use of animals in research.

Some non-clinical studies performed at Case Western Reserve University (CWRU) were not in strict compliance with the letter of the Good Laboratory Practice Regulations. Procedures at the university, however, conform to the spirit of the regulation. Studies were conducted following defined protocols, written records were kept of the study results, and generally accepted standards of scientific research were followed. Research studies were also subject to peer review by the agency funding the work. The review process served to establish the worthiness of the studies and the scientific merit of the methods and the procedures employed. Many of the non-clinical studies were conducted as part of the academic program in biomedical engineering at CWRU, and as such, were subject to the careful procedures and quality controls which are key principles of the GLP regulations.