Official Title:	Controlled Trial of 3,4-Diaminopyridine in Lambert-Eaton Myasthenic Syndrome (LEMS)
NCT number:	D04013
Document Type:	Study Protocol.
Date of the Document:	Sept. 23, 2008

Notes:

Protocol states that no statistical analysis would be done on the data.

Study Protocol dated Sept. 23, 2008. Last IRB approved on April 25, 2018

PROTOCOL

Treatment of Lambert-Eaton Syndrome With 3,4 - Diaminopyridine

Objectives:

To provide access to 3,4 - diaminopyridine (3,4 - DAP), a drug which has been demonstrated to be effective in treating the weakness associated with Lambert-Eaton Myasthenic Syndrome (LEMS) but is currently not approved by the FDA for use in the United States.

Background:

LEMS is a rare autoimmune cause of a defect in neuromuscular transmission. The disorder is clinically characterized by fluctuating muscle weakness, hyporeflexia and autonomic dysfunction. More than half of LEMS cases are associated with a malignancy, usually small cell lung cancer. These paraneoplastic cases progress more quickly than primary autoimmune LEMS. An overlap syndrome with other autoimmune diseases is often detected in LEMS patients.

The defect in LEMS is immune-mediated loss of voltage-gated calcium channels at the presynaptic membrane of the neuromuscular junction. Approximately 50% of patients with LEMS have detectable serum antibodies to the voltage-gated calcium channel. The decreased number of calcium channels leads to a decrease in calcium influx which, in turn, leads to a decrease in quantal release of synaptic vesicles containing acetycholine. Thus, the safety margin for neuromuscular transmission is lowered.

3,4 - DAP is effective in LEMS because it increases calcium influx into the nerve terminal by blocking potassium efflux and thereby prolonging the presynaptic action potential. 3,4 - DAP is less likely to provoke epileptic seizures than its precursor, 4-aminopyridine, because it is less able to cross the blood-brain barrier. 3,4 - DAP is effective in increasing strength and improving autonomic symptoms in LEMS patients of both the primary autoimmune and paraneoplastic etiologies.

Although 3,4 - DAP has been found to be efficacious in the treatment of LEMS. It is not currently FDA-approved for use in the United States. The investigator is requesting access to this drug for patients under FDA guidelines such that the patients can be formally monitored for efficacy and side effects. Potential significance of this study is that it will add to existing data regarding efficacy and

safety of this drug. This information may then be used to help determine whether or not 3,4 - DAP will be approved for general use.

Research Design and Methods:

Patients with clinically-confirmed LEMS will receive 3,4 - DAP by mouth in slowly increasing doses. Treatment will begin with 5mg three times a day. A common final dosage is 15mg four or five times a day. A common final dosage is 15 mg four or five times a day, as clinically needed, and if tolerated. The upper limit is a total of 100 mg/day. Patients will be monitored for strength and side effects via routine clinic visits at initial intervals of one month, increasing to intervals of six months as permitted. Results of treatment and adverse events will be reported to the FDA and Jacobus Pharmaceutical Company, Inc. Treatment will be continued indefinitely if a good clinical response is achieved and side effects are tolerable.

Patients will be allocated into one group only. 3,4 - DAP will be made available to patients with clinically diagnosed LEMS, who meet all of the criteria set forth in this protocol, and who, in the investigator's opinion, can be reasonably managed while taking the drug. No statistical analysis will be done on any data collected. Data will be made available to the Food and Drug Administration and Jacobus Pharmaceutical Company, Inc.

3,4 - DAP will be administered to patients who are on the full dosage of pyridostigmine bromide (Mestinon) since concurrent pyridostigmine will smooth out and lengthen the duration of effect.

This study will be conducted in the Neurology clinic at this hospital or practice, Jacobus Pharmaceutical Company, Inc. will supply 3,4 - DAP to the physician's office or hospital pharmacy; the pharmacy or physician's office will then dispense the drug to patients. No medication will be dispensed directly to the patient.

For admission to the study, patients **must meet** the following:

A. Be 18 years or older, diagnosed with LEMS
B. If female, have negative pregnancy test and, it premenopausal, be willing to practice an effective form of birth control during the study.
C. Tested and found by ECG not have a prolonged QT_c syndrome
D. Agrees to have a second ECG at the time of peak drug effect.
E. Has understood and signed the Informed Consent.

A patient **will be excluded** from the study if he/she:

A. Is known to have a sensitivity to 3, 4 - DAP
B. Has a history of past or current seizures or of severe asthma
C. Is believed by the investigator to be unable to comply with the protocol
D. Is unable to give informed consent

No patient will be excluded based on race, ethnicity, gender or HIV status.

Patients will be expected to comply with monthly office visits and blood tests (CBC, electrolytes, glucose, liver function tests, BUN, creatinine) for the first three months of treatment, and then at least once every six months thereafter.

Potential Side-Effects:

3,4 - Diaminopyridine is a potassium channel blocker. Potassium channel blockers have the theoretical potential of lengthening the QT_c interval. To date such lengthening has not been observed, but the patient population is limited. In this study patients are required to have a baseline ECG and a normal QT_c interval. As soon as the appropriate dosage has been selected the patient is to have a second determination at the time of peak drug effect, usually two hours after the last administration. Between one and three months later a second repeat determination at the peak drug level is expected.

In a series of patients with LEMS who were treated with 3,4 - DAP (Annals New York Academy of Sciences 841:811 - 816 (1998), the following side effects were noted: circumoral paresthesias, epigastric distress, and difficulty sleeping. Rare patients in this study experienced a seizure while on a dose of 100 mg 3,4 - DAP per day or while taking lower doses but with a concomitant brain tumor. Based on clinical data published to date, adverse reactions have generally not resulted in discontinuation of medication.

If a patient experiences a seizure, the 3,4 - DAP will be held for one day and then the dose will be lowered. The patient will be evaluated with an imaging study of the brain (MRI or CT scan) and will have an electroencephalogram and a clinical evaluation to determine whether or not there may be another cause for the seizure. If the patient has a second seizure on a lower dose of 3,4 - DAP, the drug will then be discontinued.

Alternative Treatments for LEMS:

Alternative treatments for LEMS patients include agents that are directed at the immunopathogenesis of the disease, such as prednisone, azathioprine, cyclosporine or cyclophosphamide. These medications all have significant side

effects, are all of limited benefit, and may not become clinically efficacacious for several months (therefore are not helpful in the acute setting).

IVIG and plasma exchange are more rapidly effective. For LEMS patients, however, the benefits of these treatments are short lived. Symptomatic therapy designed to augment neuromuscular transmission is important in the acute setting. Inhibitors of acetylcholinesterase (Mestinon) are of benefit, although not to the degree observed in myasthenia gravis. Guanidine hydrochloride offers some benefit, but is poorly tolerated, causing renal and hematological side effects, and is rarely used.

Safeguards:

Clinical effectiveness (increased strength) and side effects of 3,4 -DAP will be monitored in patients during clinic visits. Blood tests as mentioned above will be performed to monitor for as yet undescribed adverse events. Patients experiencing adverse effects will have access by phone to a neurologist 24 hours per day, as would any patient under neurologic care. Such patients can be seen immediately in the clinic or emergency if necessary. Treatment with 3,4 - DAP will be terminated if the medication does not result in increased strength or its side effects are not tolerated. A baseline ECG and a second ECG at the time of peak drug effect will monitor for an effect on the QT_c interval. The interval is expected to remain normal. If the QT_c interval is abnormal prior to treatment the medication is not to be given. If it lengthens while on drug it is to be stopped.

Costs and Payments:

3,4 - DAP has not been approved by the FDA for use in the United States in treating the muscle weakness associated with LEMS. 3,4 - DAP is being made available free of charge by the Jacobus Pharmaceutical Company, Inc. (Princeton, New Jersey 08540) for patients with LEMS. Physician's and institutions receiving 3,4 - DAP for their patients have received approval (IND numbers) from the Food and Drug Administration.

Patients will continue to receive their usual routine care for LEMS including blood tests. Patients will not be paid for their involvement in the protocol.

Confidentiality of Records:

All records associated with subject's participation in this study will be subject to the usual confidentiality standard applicable to medical records, and in the event of any publication resulting from the research, no personally identifiable information will be disclosed. The Jacobus Pharmaceutical Company, Inc. will

receive a record of each patient's name, address, telephone number and the clinical details associated with 3,4 - DAP administration. FDA representatives may review the medical records.

Investigator's Qualifications:

Dr. Jeffrey Cohen is a staff Physician at the Department of Neurology, Dartmouth Hitchcock Medical Center. He specializes in the treatment of patients with neuromuscular disorders. He has extensive experience with caring for patients with neuromuscular junction disorders.