

7-05-1064

Proposal 77-5

CLINICAL INVESTIGATION STUDY PROPOSAL

INSTITUTION: Naval Regional Medical Center, Philadelphia, Pa. 19145

TITLE OF PROJECT: Monoamine Oxidase: Clinical Use as an Indicator of Incipient Hepatic Fibrosis

INVESTIGATORS:

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A. OBJECTIVES:

To determine the clinical usefulness of the determination of plasma monoamine oxidase (MAO) and its isoenzymes in the detection of varying degrees of fibrosis in the human liver.

B. BACKGROUND:

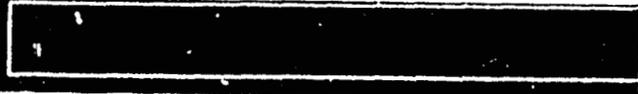
The over-all goal of a former CIP Project (5-05-532R) was to gain greater insight into the process and timing of formation of cirrhosis in disease states of varying etiologies, in order to produce a clinical test that will accurately detect incipient hepatic fibrosis. This test would allow monitoring of the course of such fibrosis during the development of methods with potential for altering or preventing hepatic fibrosis. Such a test does not exist.

To this end, work already completed at this institution has shown that patients with histologically proven hepatic fibrosis have serum MAO values that are significantly elevated with respect to normals and patients with acute liver disease (hepatitis). Additional work has shown that the plasma MAO in a patient with hepatic fibrosis (hemochromatosis) has different intrinsic molecular properties than normal human MAO, thus indicating the possible presence of isoenzymes.

NAV1.954182.002

Encl (99)

7-05-1064



Follow-up studies have confirmed the presence of multiple forms (isoenzymes) of MAO in human plasma (3). Separated by hydroxyapatite column chromatography, three forms of the enzyme have been designated  $\alpha$ ,  $\beta$ , and  $\gamma$ .

Further studies with plasma from patients with a chronic fibrotic liver disease (hemochromatosis) have shown that these patients have less  $\alpha$  form (40 vs 84% of total), increased  $\beta$  form (more than 25% of total) and have an additional form termed  $\chi_1$  (20%). (4)

The most recent work presented at the AASLD in Chicago this fall presents animal studies demonstrating specific changes in isoenzyme patterns in developing cirrhosis similar to changes observed in human patients (4).

The techniques developed at this facility have progressed to the point where the testing of a larger group of patients has become feasible.

C. APPROACH:

1. Population:

The 10-20 patients selected for the study will be of either sex, previously diagnosed as having Hepatic Cirrhosis, Laennec's type by liver biopsy either percutaneous or at laparotomy.

Prior to selection, each patient will have a physical examination by one of the investigators (TJH) as well as the following laboratory tests: complete blood count, platelet count, prothrombin time, partial thromboplastin time, SGOT, SGPT, alkaline phosphatase, albumin, total and direct bilirubin.

Patients will be excluded from the study if any one of the following are present:

- a. Physical exam indicating recent deterioration of the patient's general health either secondary to Laennec's Cirrhosis or, intercurrent disease.
- b. Hematocrit less than 38%.
- c. Prothrombin time elevated more than 4 seconds over control.
- d. Total bilirubin greater than 2.5 mg. %.
- e. Liver enzyme picture compatible with acute hepatic inflammation.

Written informed consent will be obtained if patient is selected for the study. (Form attached)

2. Methods:

By prior arrangement with the blood bank, one to four patients will undergo standard plasmapheresis to obtain a total of two units of plasma (500 cc).

As precautionary measures, a physician (TJH) will be in attendance during the entire procedure for all patients. In addition, plasma expanders and an emergency kit will be available in the blood bank for immediate use.

Plasma MAO and MAO isoenzyme levels will be obtained via published methods. (2-4).

Clinical data will be collected using a standard form. (Form attached)

All patients will be admitted to the hospital and observed for 24 hrs. following the plasmapheresis.