The Use Of Sertraline In Neurocardiogenic Syncope

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A. Study Purpose And Rationale

Recurrent unexplained syncope is a common and frustrating clinical problem, which accounts for approximately 3% of all adult emergency room visits and 6% of all admissions to the adult medical service. (Kapoor, et al, 1983) Many of these recurrent unexplained syncopal episodes are felt to be secondary to transient periods of neurally mediated hypotension and bradycardia, i.e. "vasovagal" syncope.

Moving to the upright position is accompanied by a pooling of blood in the legs, and thus decreased blood return to the left ventricle. In the normal individual, this change of position leads to increased sympathetic tone, with resultant vasoconstriction and positive inotropy and chronotropy, and blood pressure is maintained. In patients with neurocardiogenic syncope, however, mechanoreceptors in the heart are activated by the increased inotropy, and as the ventricle contracts vigorously against an underfilled chamber, the body reacts to the perceived overdistension of the ventricle by decreasing the sympathetic tone and increasing the parasympathetic tone, which is the Bezold-Jarisch reflex. This results in peripheral vasodilatation, hypotension, and bradycardia, and subsequent syncope. Patients generally recover quickly from this event, as perftision is restored quickly by the horizontal position.

The diagnosis of neurocardiogenic syncope centers on the history, combined with the head-up tilt table test (HUTT). Briefly, HUTT is done by placing the patient on the table in the horizontal position, and then changing to a 60 or 75 degree angle witli the head up, with continuous monitoring of surface electrocardiogram (EKG), blood pressure (BP), and heart rate (HR). In patients with neurocardiogenic syncope, after a delay of 10-30 minutes, syncope or presyncope occurs, generally accompanied by an acute drop in blood pressure and/or heart rate, and sometimes with a sinus pause.

The several available treatments for neurocardiogenic syncope, while effective for some patients, are bv no means satisfactory. Beta blockers are used to decrease inotropy and thus block the afferent limb of the Bezold-Jarisch reflex. Transderinal scopolamine blocks the efferent parasympathetic output. FILidrocortisone has been used to improve volume status and sensitize alpha adrenergic receptors. Disopyramide has anti -choli ne rgic activity and has intrinsic negative inotropic actions, and has been effective ill some patients. A new agent, tile vasoconstrictor initodrine, has recently been approved, flowever, this agent has obvious limitations in patients with co-existing heart disease. However, many patients have syncope refractory to tile above treatments, and a permanent pacemaker can be inserted, however, this is obviouslv more effective in patients with a greater contribution to their syncope of bradveardia rather than vasodilatation. There are inany patients, however, who do not have relief from frequent syncopal attacks with any of the above therapies.

The exact nature of the Bezold-Jarisch reflex and the reasons for its dysregulation in some patients has been an area of active investigation. Levels of circulating catecholantines have been shown to be altered during HUTT (Sra, 1994-1 Bhargava. 1996), which nlay contribute to syncope in addition to the more wellestablished vagal reflex arc. Additioilally, aninial studies of acute blood loss have demonstrated that decreased levels of serotonin, via nietllysergide, a serotonin receptor blocker, blunt the acute drop in blood pressure induced by hemorrhage. (Morgan, 1998) The hypotension accompanying heiriorrhage may occur via the same Bezold-Jariscli reflex, Mlore recently, several studies have demonstrated the utility of serotonin reuptake inhibitors in the treatment of refractory neLirocardiogeiiic syncope.

The investigation of serotonin and its centrally mediated effects is fraught with difficulty. Peripheral blood levels of serotonin do not reflect changes in intracerebral activity. In aninial studies, measurements of intracerebral serotonin activity is accomplished via a nucrodialysis technique which involves stereotactic surgical placement of the dialysis membrane, all interventioti obviously not suited to

Iminari trials. (Malagie, 1995) Thus, tile human investigation of serotonin and its reuptake inhibitors (SSRIs) has proceeded "ith straightforward clinical trials of SSRIs in the relevant patient population, and more complicated trials of HUTT with measurements of surrogate markers of central serotonin activity.

Several studies (Grubb, 1993 *, 1994, Matzen, 1993) have demonstrated the efficacy of SSRIs in refractory neurocardiogenic syncope. These studies report a 50% response rate to fluoxetine or sertraline. However, there are also case reports of neurocardiogenic syncope being made worse by treatment with SSRI. (Tandan, 1997) Thus, "neurocardiogenic syncope", as currently conceptualized, may be a heterogeneous disorder, thus further complicating its investigation. The mechanism of response to SSRIs in those patients who become HUTT negative is presumed to be as follows: SSRI treatment leads to increases serotonin transmission in the brain via blocking serotonin reuptake in the afferent nerve terminal. This increased transmission leads to a down-regulation of the serotonin receptors, and thus a blunted response to serotonin. Given that serotonin blockers lead to decreased hypotension in hemorrhagic animals, any mechanism that decreases responsiveness to serotonin may lead to higher blood pressure.

Recently, Theodorakis, et al (1998) pursued an interesting study in which they used clormpramine, a tricyclic antidepressant with marked serotonin reuptake inhibition, to study the central responsiveness of the serotonergic system. The release of prolactin from the pituitary is under partial control of serotonin. The administration of clormpramine will acutely raise central serotonin levels, leading to a release of prolactin, and a rise is peripheral prolactin levels. Thus, then change in prolactin level in response to this intervention is a surrogate marker for the sensitivity of the central nervous system to serotonin. In their study, Theodorakis et a]. demonstrated that patients with positive HUTT had greater responsiveness of the CNS to clormprainine challenge, and thus concluded that serotonergic activation plays a role in neurocardiogenic syncope.

In the current study, I propose to investigate the effects of chronic SSRI use on neurocardiogenic syncope and on the responsiveness of the central nervous system to clornipramine challenge.

B. Study Design And Statistical Analysis

a. Study Arms

The study will have two arms, a study group composed of patients with syncope, positive HUTT, and continued symptoms despite treatment with appropriate therapy including betablockers, scopolainine, etc. The control arm will be individuals with no history of syncope.

b. Numbers of Subjects

14 patients in the study arm, and 8 in the control arm. Approximately 50%' of the study arm would be expected to have a clinical response to the sertraline. Assuming that the change in the slope of the cortisol level in responders will go from that of patients with typical neLtrocardiogenic syncope to that of patients without neurocardiogenic syncope, this large change "I be easily demonstrable via t-test analysis.

c. Randomization

Patients will be divided into control and study groups based on their past medical history. No placebo will be needed in this trial as each patient will be his or her own control.

d. Crossing Over

All patients will have initial testing off medication and then repeat testing on medication.

e. Statistical Analysis

The primary endpoints are HUTT results and change in slope of peripheral blood prolactin level. The HUTT results will be analyzed via Chi square. With an expected response rate of 50% in the study group, 14/14 initially positive tilt tests will then become 7/14 positive. The reproducibility of HUTT is approximately 70%, and the anticipated compliance with the sertraline is 90%, and thus 14 study subjects is a sufficient number to give a statistically significant result if the effects of sertraline are as anticipated.

The peripheral serum prolactin level will be measured several times during HUTT both before and after treatment with sertraline, as detailed below. Thus, for each patient, a coefficient of the slope of PRL conc v. time during clonlipramine challenge will be determined by regression analysis. In the study group, it is anticipated that before treatment, that slope will be approximately +0.30 ng/ml PRL / min, and after treatment +0. 10 uig/nil PRL / min. The exact patient to patient variation in this slope is difficult to discern from previous studies, but given the almost three-fold anticipated change, analysis via t-test techniques will show a statistically significant result if the effects of sertraline are as anticipated.

In the control groups, it is not anticipated that there will be any substantial change in their response to prolactin challenge after treatment with sertraline. However, this is based on conjecture only.

C. Study Procedures

a. Procedure

The study will require to visits to the study center by each patient. Each visit will consist of two parts. First, each subject will undergo HUTT. For this procedure, the patient will be strapped to the RUT table, initially in the supine position, with continuous EKG recording, HR recording, and noninvasive BP monitoring. The patient is then moved to a upright position of 60 degrees from the horizontal. If the patient experiences syncope or pre-syncope, (s)he will be returned to the horizontal position, and the test is considered positive. If there is no such result after 30 minutes, intravenous access will then be obtained and an infusion of isoproterenol will be given at a rate of 2~tg/min over 10 minutes. If after an additional 30 minutes there is no syncope or presyncope, the test will be considered negative.

The second portion of the visit will consist of the clornipramine challenge. Continuous EKG and BP monitoring will be continued. Using the previously obtained IV access, patients in the supine position will have 5 cc of peripheral blood sampled at time 0, 10,. 20, and 30 minutes, From minutes 0 to 10, 25 mg of clontipramine in 150 cc of NS will be administered.

Patients will then be given the standard starting dose of sertraline 50 mg PO QD. The second study visit will be 6 weeks to 2 months after the initial visit, and patients will undergo the same protocol as the first visit. Each visit should last no longer than 2-3 hours.

b. Number of visits and procedures

Two visits and two tilt table tests and clomipramine challenges, as detailed above. This is more testing than standard of care would dictate as necessary, however, a total of only two venipunctures would be required, and the remainder of the testing is noninvasive and done in a secure environment with a physician present at all times.

c. Duration of study

Each patient's participation in the study would last for two months. Given the frequent occurrence of syncope in the patient population at this hospital, it is anticipated that subject recruitment could be completed within several months.

D. Study Drugs

a. Clorniprainine

Is currently approved for use in the US as an antidepressive. As described in the introduction, it is a potent central serotonin reuptake inhibitor, and it has been used in several previous studies to elicit prolactin release as a measure of central serotonergic responsiveness. In previous studies (Theodorakis, et al., 1998), the major side effect was Gf discomfort. which occurred in 40% of subjects. 95% of those with side effects were able to complete the protocol. There were no significant changes in any heiriodynainic parameters, although there was a tendency towards lower HR.

Clonuprarnine will be administered via IV infusion, as has been done in other studies, in doses previously used.

b. Sertraline

Is currently approved and tinder widespread use as an antidepressive in the US. As described in the introduction, it is a SSRI, and is believed to act via down regul ati on of serotonin receptors, and In previous studies in patients with syncope, approximately 10% of patients discontinued sertraline, due usually to GI complaints and to headache. Serious complications of sertraline therapy are extremely rare, Notably, there have been case reports of SSRIs increasing the frequency of syncope in patients with preexisting disease. Patients will need to be warned of this possible effect and to contact the investigators immediately if there is any increase in their symptomatology.

Sertraline will be administered through the standard PO route at the common beginning dose in all patients.

c. Isoproterenol

Is currently approved for a variety of cardiovascular indications including increasing the sensitivity of HUTT, as itiArill be used in this study.

E. Medical Devices

No devices will be used in this protocol.

F. Study Questionnaires

One questionnaire \vill be given to patients at each visit dealing -,xith their syniptnins during the previous nionth-frequency, severity, and, at the second visit, and perceived change in their syniptornatology.

G. Study Subjects

Patients in the study arm will be recruited from patients referred for HUTT testing for recurrent syncope. Patients in the control arm will be recruited from hospital and local community and age- and sex-matched to the study subjects.

a. Exclusion criteria:

- History of SSRI, tricyclic, or other anti-depressant use.
- History of recent use of drugs effecting serotonergic system: buspirone, surnatriptan, risperdone, ondansetron, cisapride, and related medications.
- Structural heart disease (wall motion abnormalities, known CAD,
- va1vular disease)
- Explained syncope
- Hypertension
- Thyroid disease
- Pregnancy
- Other major medical problem-. neoplasm, diabetes, Hx of CVA.

b. Inclusion criteria:

i. Study

- Unexplained syncope with positive HUTT refractory to medical treatment with beta blockers and scopolamine
- Negative work-up for source of syncope including EKG, ECHO, Head CT, and EEG.

ii. control:

- No history of syncope.

c. Minority subjects:

Given the high minority population served by this hospital, it is

anticipated that many of the subjects will be from minority groups. Special efforts will be made to increase awareness of this study among medical liousestaff who see patients in the AIM clinic, which is almost entirely minority.

d. Number of Subjects:

As detailed above, it is anticipated that 12 study subjects, and 6 control subjects will be sufficient.

H. Recruitment Of Subjects

For study patients, their primary care physicians will be contacted after they are referred for HUTT, and, after permission is granted, the investigators will then arrange to meet with the patient to discuss enrolling in the study. For control patients, flyers will be given to primary care providers to refer patients to the investigators for the control arm of the study.

I. Confidentiality Of Study Data

Study information pertaining to individual patients will be coded and stored in the secure offices of the investigators.

J. Potential Conflict Of Interest

The investigators have no interest, proprietary or otherwise, in cloniipramine, sertraline, isoproterenol, or the manufacturers of HL7T equipment.

K. Location Of The Study

Both visits will occur, as will all testing, in the HUTT lab on HP-10.

L. Potential Risks

As stated above, this study is for patients with syncope refractory to medical therapy. Thus, while the patients have only a 50% chance of responding to the therapy in this study, there is no current effective therapy available for them.

There is a small risk that treatment with sertraline may lead to worsening of symptoms, i.e., more frequent syncope. Study subjects will be instructed to call the investigators for any increase in their symptoniatology, at which time the patient and investigators will decide whether to continue the study in that patient.

M. Potential Benefits

For approximately 50% of the study subjects, it is anticipated that treatment with sertraline will lead to a resolution of their symptoms. Subjects may or may not benefit as a result of their participation in this study. The results of this study may make it easier for physicians to identify those patients with syncope who will respond to SSRI therapy. Additionally, the study may lead to new insights into the mechanisms of neurocardiogenic syncope, which could potentially lead to new and more effective therapies in the future.

N. Alternative Therapies

There are other therapies for neurocardiogenic syncope, however, some patients do not have a good response to any of them. The patients for this study should have continued symptoms despite

treatment k,,4th adequate doses of the several medications approved for neurocardiogenic syncope, as detailed in the introduction.

O. Compensation To Subjects

Study subjects will not need compensation, as their ongoing symptoms will most likely make them willing to participate in a study such as this.

Control sub~jects. being free of disease, will be compensated $50 for each visit.

P. Costs To Subjects

Other than time, there should be no costs to the subjects.

P. Minors As Research Subjects

N/A

Q. Radiation

N/A

R. Bibliograpry

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