

OBJECTIVES

The hypothesis of this study is that schizophrenics have rCBF patterns which differ between resting and stimulated conditions. The resolution now available with SPECT may also demonstrate differences between the pre-treatment and post-treatment conditions. The objective of this study is to test this hypothesis under four conditions:

- 1a. Resting state at baseline
- b. Stimulated state at baseline plus 3 days

- 2a. Resting state follow-up after 3 to 4 weeks of medication
- b. Stimulated state follow-up plus 3 days

The hypothesis will be verified or rejected based on interpretation of the rCBF images by a Nuclear Medicine physician, who will be blinded to the four study conditions.

ENCLOSURE (1)

APPROACH

The dosage of radio tracer for the scan imaging will be 5 millicuries HIPDM IV for each of the two resting non-stimulated scans and 5 millicuries HIPDM IV for each of the two Wisconsin Card Sort stimulation scans which will follow the resting scans by 2 to 3 days. Total dosage of HIPDM will thus be 20 millicuries, divided into 4 doses over a period of approximately 1 month. I-123, which is the radioactive portion of HIPDM, is approved for clinical usage in the Nuclear Medicine clinic in its pure form or in combination with hippuran. I-123 in the HIPDM pharmaceutical is, however, a phase III investigational drug. An IND request is being submitted to the FDA concurrent with this protocol. A copy of the IDCI toxicity data is attached.

Blood levels for anti-psychotic medications will be drawn at baseline to verify medication free status. At week four blood levels for anti-psychotic medication will be drawn to verify achievement of therapeutic blood levels.

The sampling size will be approximately 16 patients. All patients will be from the Psychiatry Service at the Bethesda Naval Hospital. They will be entered into the study from those consecutive admissions who have a Diagnostic and Statistical Manual (DSM-III) diagnosis of schizophrenia and who agree to voluntarily participate. A psychiatrist, other than the one who obtains the informed consent, will enter a progress note verifying the competency of the patient to give informed consent for the study. This progress note will be written and/or co-signed by a credentialed staff psychiatrist. The expected rate of admission to the Psychiatry Service with a diagnosis of schizophrenia is approximately two per week. If 50% of these consecutive admissions agree to participate, it is anticipated that one patient per week will be accessioned into the study over 16 weeks.

An intersecting coronal and transverse slice from the scan will be compared to each of the four clinical conditions using a 4x2 ANOVA. The nature of the SPECT together with the necessity that the untreated (drug free) condition must precede the treated (drug exposed) measurement dictates adoption of a repeated-measures within-subjects design. The study is designed for an alpha level set at a conventional value of .05 (5% chance of Type I error). Power function analysis using Phi (sub A) yields a less than 5% Type II error likelihood under the following assumptions: sample size=16; 4*2=8 outcome measures; variance S/A=20% of expected overall mean level of measured emission and an experimental effect size=20% of overall mean (both deliberately set more stringently than values typically obtained in clinical SPECT). The Phi value exceeds 2.50. Calculations are not presented, since the analysis requires entry of the Phi value into power-function graphs not readily reproducible here. Ch.4, section 3, pp.70-73 and the upper section of Appendix A, Table A-2, p.552 of Keppel provide the procedure used to determine power and sample size (16).

Psychiatrists who provide clinical care and the patients themselves will be aware of the clinical condition grouping, but procedures will be implemented to avoid contact with the Nuclear Medicine physician who is interpreting the scan. Psychiatrists and patients will thus be blinded to the scan results and the Nuclear Medicine physician will be blinded to the clinical condition group. The overall study design is thus double blinded with self paired controls.

Inclusion criteria are right handed males, between the ages of 18 and 38 inclusive, with a DSM-III diagnosis of schizophrenia established by a credentialed staff psychiatrist.

Initial exclusion criteria are non-psychiatric medical disorder, organic brain syndrome, previous diagnosis of alcoholism, a current score of greater than or equal to 6 on the Michigan Alcoholism Screening Test (attached), a self reported consumption of greater than 2000 ounces of absolute alcohol per year, or any self reported history of illicit drug usage. During the course of the patient's hospitalization, there may be additional psychological testing to assist in diagnostic evaluation. The patient will also receive on going clinical evaluation by psychiatrists, psychologists, psychiatric nurses, and other members of the health care team. If, as a result of additional psychological testing and additional clinical evaluation, the patient's discharge diagnosis is changed from the initial diagnosis of schizophrenia; then the patient will be excluded from the schizophrenic study group. The number of dropouts and the number of patients who refuse to participate will be noted. An attempt will be made to replace any dropout with a new patient to keep the total number in the group as close as possible to 16.

The principal investigator is responsible for coordinating data accumulation from the associate investigators. No adverse effects from the 5 millicuries of HfPDM per scan are expected; if any were to occur, they would be noted by the physician conducting the scan and communicated to the principal investigator.