Protocol for Determining Minimal Effective Doses of Psychotropic Chemicals in Humans

SMUEA-CR-MV

10 Jul 64

Dir of Med Res | Ch, Clin Res Div | LtColBottiglieri/rmv/23293

Per your instructions, a proposed protocol for determining minimal effective doses of psychotropic chemicals in humans has been prepared and is enclosed herewith. An attempt was made to design this protocol so that it could be applicable to studies here as well as at Holmsburg Prison.

Incl
as

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DRAFT 9 July 1964

SUBJECT: Protocol for Determining Minimal Effective Doses of Psychotropic Chemicals in Humans

I. Purpose

To establish standard basic procedures for determining the threshold dose or minimal effective dose (MED) of various drugs, chemicals or compounds which have an effect on the mental and physical capabilities of man.

II. Background

It is an important requirement to screen by pharmacologic studies candidate chemical warfare agents in order to determine whether the MED of such agents is small enough to allow the agent to be considered as practical in chemical warfare. Quantitative as well as qualitative changes in mental and physical functions must be determined by a preliminary screening procedure in humans before extensive pharmacologic study can be carried out with a compound being considered as a potential chemical warfare agent. MED testing programs are presently being conducted at Holmsburg prison under a contract with the University of Pennsylvania and by the personnel of Clinical Research Division, Directorate of Medical Research, USAEA CRDL. In order to better understand and interpret results of such testing, it is important that a standard procedure for these tests be followed by all concerned.

III. Materials and Methods.

a. Compounds to be Studied

Complete toxicological and pre-clinical information on each candidate agent will be submitted to the Directorate of Medical Research for evaluation pertaining to the feasibility and safety of testing such agents in man.

When it is decided that an agent should be tested in humans a quantity of the material and a preparation fit for human administration will be delivered to the Directorate of Medical Research, who will in turn be responsible for distributing such material to the appropriate testing facility. A brief protocol will then be prepared by the responsible investigator outlining the specific details of the test program to be used for each individual agent. Such protocols will be approved by the Director of Medical Research or his designee.

b. Selection of Subjects

1. A cooperative, interested, intelligent, stable, well-motivated subject produces more uniform responses but such ideal subjects cannot always be found. At least the best ones can be chosen by a sequential process of elimination as follows:

(a) Age - 21 to 35 years

(b) Duration of Availability for Testing - 6 months or more at Holmsburg prison, OR Four weeks or more at Clinical Research Division.

(c) Education - 8+ years

(d) Ability to perform arithmetic problems - 20+

(e) Satisfactory MMPI Personality Profile

(f) Satisfactory Psychiatric Interview

(g) Acceptable Physical Condition

(h) Acceptable Reports of Laboratory Studies

2. Physical examination and laboratory tests can be performed by responsible personnel at each prospective testing facility. At Holmsburg a

group of 30 subjects can be selected at three month intervals. Repeated testing of subjects following appropriate waiting periods will not impose a hardship since the doses used will be so low.

c. Experimental Design

1. General. Agents under consideration may be expected to produce both autonomic and central nervous system effects, though not necessarily to the same extent with each agent. In some cases evidence of peripheral cholinergic blockade will appear before the noticeable effects on mentation or state of consciousness. However, the reverse may also occur. In general, it is the central nervous system effectiveness that makes these compounds of military interest; therefore, the threshold response of principle importance should be one related to intellectual performance. On the other hand, it is important to select response criteria for autonomic effects which will, within a safe time period, dictate the cessation of testing at a non-hazardous level. If a threshold CNS response has not been observed by the time a dangerous peripheral response level is reached, it is doubtful that this agent would be considered of further military importance. Personnel limitations as well as safety factors must be borne in mind when designing a particular study protocol. Continuous observation by professional personnel throughout the duration of response cannot be expected so it will be necessary to arrange for such observation during a short period (4-6 hours) coinciding with the peak period of action.

d. Definition of the MED50: For purposes of this study, the following is proposed as an operational definition: "The MED50 is the dose which will (as computed by probit analysis) cause at least a minimum response in at least 50% of the population represented by the sample. A minimum response

is, in turn, defined as a mean per cent score on the Numerical Facility test of less than 75% (mean = mean of 3 lowest scores obtained during 4 hour experimental period selected to correspond to time of peak action).

If an elevation of heart rate to above 100 beats per minute, an oral temperature elevation to above 100° F. or any other distinct evidence of toxicity should be consistently observed at dose levels insufficient to produce minimal response as defined above, further testing with the agent will be suspended pending review by the project officer or his designated representative.

e. Dosages. Dose levels should be determined primarily from the standpoint of safety and, secondly, for statistical efficiency. The general approach as used in probit analysis would be as follows:

1. Dose levels will be arranged in geometric series; i.e., 40% increments between successive dose values.

2. Two subjects will be tested at each dose level until an approximate MED is arrived at.

3. Two or more additional subjects will be exposed to the approximated MED and if roughly half of the total number so exposed demonstrate the minimal response, 4 or more exposures each will then be conducted at doses 20% above and below this approximate MED. This will normally provide a sufficient range and sample size to permit a statistically adequate estimate of the MED50.

4. Doses will be given in ascending order -- not at random.

f. Methods of Observations.

1. Baseline: Following selection, subjects will undergo baseline measurement of skill in arithmetic, using the numerical facility test forms provided. Ten 3-minute test sessions, distributed over a 2-day period are recommended as a minimum practice series, the baseline being computed by averaging

the 5 highest scores obtained. Subsequent test scores are expressed as a percentage of this baseline.

Baseline heart rate, blood pressure, ~~respirations~~ RESPIRATORY RATE, pupil size and oral temperature will also be obtained during the same general period. It is advisable to repeat PRE-TEST heart rate and blood pressure determinations at least 10-12 times at various times during the day and evening, both to increase the reliability of the control values and to reduce the psychological reaction to these procedures ~~which otherwise often contaminates~~ DURING the early part of the experimental period.

To increase familiarization and relaxation ~~when possible~~, subjects should WHEN POSSIBLE spend the night prior to the FIRST injection of a test compound in the room, cell or ward where the test will take place. A light breakfast, eliminating fat-containing foods, should be consumed at least one hour prior to injection. Intellectual testing and physiological measures should be made in a consistent manner in a quiet environment free from interruptions or distractions. If an unusual and sudden change in performance in the numerical facility test should be encountered, the subject should be further investigated with respect to his physical condition, alertness and motivation, and then tested again 5 minutes later to confirm the validity of the discrepant results. If the apparent discrepancy persists, the first score should be regarded as valid, and the second discarded, but if the re-test shows a relative change of more than 25%, a third test should be given after another 5 minutes and the 2nd and 3rd values averaged.

2. Following administration of test agent, during the 4-hour period surrounding the presumed peak of action, the NF test should be administered

once each hour, preceded by a 60-second measurement of the supine resting heart rate, AND THE PUPIL SIZE. the oral temperature. A note should be made by the nurse or technician regarding the subject's general appearance, AND behavior along with a verbatim record of the subject's own description of his status. This note should be made hourly, following the NF test. Blood pressure should be taken if heart rate is above 100 or below 50, or if temperature is above 100.0° F. The physician in charge will presumably check the status of the subjects frequently, and make whatever clinical examination seems indicated.

Before and after the 4-hour period of peak action, observations may be left to the discretion of the physician in charge. Subjects may be returned to their usual areas if he is satisfied that no significant clinical effects are in evidence after the peak period has passed. Difficulty with near vision frequently persists longer than other symptoms, and need not occasion concern unless it is marked.

3. Reports. A chronological clinical record may be kept for each subject during the test, on forms provided. To facilitate the reduction of numerical data, the experimental values relevant to the study may be summarized on a data sheet such as depicted in the attached sample.

Name: Jones, R. Agent: K
Date: 10 Aug 64 Dose: e

Experimental Time	Real Time	Heart Rate	NF% Score	Temp (oral) ° F.	Pupil Diam. mm.
0600	1200	76	90%	98.8	4
0700	1300	88	81%	99.2	5
0800	1400	78	80%	99.0	4
0900	1500	74	76%	98.8	4
1000	1600	68	90%	98.6	4

Average of 3 lowest NF scores = 79%

Response is: Negative

4. All reports of test results from Holmsburg prison will be forwarded to the project officer for interpretation and statistical analysis. Reports of individual tests performed at the Clinical Research Division will be kept by the responsible Branch Chief until sufficient data on each agent can be obtained to allow for the preparation of a final report which will then be forwarded to the Chief, Clinical Research Division.