CLINICAL COMPARISON OF METHYPRYLONE AND QUINALBARBITONE AS HYPNOTICS

SEQUENTIAL ANALYSIS USED

BY

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Methypylone ("noludar"; 2,4-dioxo-3,3-diethyl-5-methyl-piperidine) is a non-barbiturate hypnotic. Stewart (1956) reported that in a dose of 200 mg. it had a hypnotic effect comparable to 100 mg. of either amylobarbitone sodium or butobarbitone. Lasagna (1956) found that 250 mg. of methypylone produced results "essentially indistinguishable" from those of 100 mg. of pentobarbitone or 100 mg. of quinalbarbitone.

The purpose of the present investigation was to compare the hypnotic effects of methypylone and standard doses of quinalbarbitone; ascorbic acid was used as a control.

Method

The patients were in general medical wards and presented a wide variety of diagnoses; there were 92 men and 36 women, and their ages ranged from 24 to 74 years. Only those who required hypnotic drugs were included in the trials. All other sedatives were withdrawn during the period of observation. The plan was similar in each of the four clinical trials. The two drugs to be compared were dispensed as white powders of similar bulk, labelled A or B, their content being unknown to patient, nurse, or clinician.

The Table lists the contents of the powders used in the four trials. If powder A was given on the first night, powder B was ordered on the second, and vice versa. To

Content of Powders A and B in the Trials

Trial No.	A	B
1	200 mg. ascorbic acid	200 mg. methypylone
2	400 " methypylone	400 " ascorbic acid
3	400 " "	200 " quinalbarbitone + 200 mg. ascorbic acid
4	400 " "	100 mg. quinalbarbitone + 300 mg. ascorbic acid

avoid bias, the order of giving powder A or B on the first of the two test nights was decided by random selection; after mixing 20 labels marked A and 20 of B, the order in which they were then drawn from a box was listed, and this determined the order of administration. When it was found during a trial that more than 40 patients were required to complete the study (51 in trial 1 and 67 in trial 3), a further list of 40 was compiled by the same method of random selection. The appropriate powder was given with a small draught of water at 10 p.m. Each patient was informed that he was receiving "a sleeping powder"; he was not told that a comparative study was in progress. The nurse was asked to observe the patient during the night and record her opinion of the soundness of sleep in the following terms: "good," "intermediate," or "poor." In the morning after the second hypnotic I asked each patient, "On which of the two nights did you have the better sleep?" Care was taken to use the same form of words, with the deliberate intention of eliciting a comparison.

The results were examined statistically by the method of sequential analysis as described by Bross (1952), and the original paper should be consulted for a detailed explanation of the statistical significance of this sequential plan. The outstanding feature of this method is that observations are charted as soon as they become available. Looking at

Fig. 1 as an example, only a stated preference between A and B is plotted as X; if a patient states that there is "no difference" between the treatments, no entry is made on the chart. If the patient states a preference for A, a mark X is placed in the square to the right of the last entry on the chart; if the preference is for B, the mark is placed in the square above the last entry. When the path of these symbols travels "north" and emerges from the boxed area, "B treatment" is superior; if beyond the "eastern" barrier, "A treatment" is superior. If the data as plotted fall into the zone between the two boxed areas, this denotes "no important difference between treatments." The clinical trial—to compare A and B—ends when the X path crosses any boundary of the boxed areas.

Results

The results are shown in Figs. 1–4, which should be read in conjunction with the Table. The first trial demonstrated no important difference between 200 mg. of methypylone

FIG. 1.—Sequential plan in trial 1, showing no important difference between the "treatments."

FIG. 2.—Trial 2, in which "A treatment" was superior to "B treatment."

FIG. 3.—Trial 3, showing 200 mg. of quinalbarbitone to be superior to 400 mg. of methypyrlyone.

FIG. 4.—Trial 4, in which there was no important difference between 100 mg. of quinalbarbitone and 400 mg. of methypyrlyone.

and 200 mg. of ascorbic acid as hypnotics. To reach this conclusion 51 patients were studied, of whom 24 stated there was "no difference" between the drugs. The second trial (Fig. 2) showed that 400 mg. of methypyrlyone was superior as a hypnotic to 400 mg. of ascorbic acid. This study required only 12 patients, as 8 stated a preference for powder A, and 4 "no difference" results were obtained. Trials 3 and 4 were planned to allow a comparison to be made of the hypnotic effect of 400 mg. of methypyrlyone with the hypnotic effect of quinalbarbitone in the commonly prescribed doses of 100 or 200 mg. The results (Fig. 3) indicated that 200 mg. of quinalbarbitone was superior to 400 mg. of methypyrlyone; the "eastern" boundary was crossed after 37 preferences and there were 30 "no difference" results. When the hypnotic effect of 400 mg. of methypyrlyone was compared with that of 100 mg. of quinalbarbitone, no important difference was found; this trial required 40 patients, 16 of whom found "no difference" between the drugs.

Discussion

There are many factors which can be considered while comparing the therapeutic value of two hypnotic drugs. The present trials have not sought to define the time of onset of hypnotic action, or its duration, the presence of disturbing dreams, or toxic effects. In this study, only the patient's judgment of the quality of sleep after different hypnotics has been used. It is interesting to note, however, that the data obtained during these clinical trials also permit of some comment on the degree of correlation existing between a clinician's assessment and that of the nurse. When the preferences for the sequential analysis were based on the nurses' considered opinions, the paths travelled in the same directions as in Figs. 1-4, but more slowly. The latter was due to the greater number of "no difference" results offered by the nurses.

Summary

The hypnotic effect of methypyrlyone (noludar) has been compared with the hypnotic effect of quinalbarbitone, using the double-blind technique. Powders of ascorbic acid were used as a control. The results were assessed by sequential analysis.

No important difference could be detected between the apparent hypnotic action of 200 mg. of methypyrlyone and the control powder. When the hypnotic effects of 400 mg. of methypyrlyone and 100 mg. of quinalbarbitone were compared no important difference was discovered.

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RATIONALE OF ANTIHISTAMINIC THERAPY IN THERMAL INJURY AN EXPERIMENTAL EVALUATION IN THE GUINEA-PIG

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Clinical trials with antihistamines in the early treatment of burns suggest that these drugs, applied locally or given orally, are useful in combating pain, blistering, oedema, and infection, and consequently in accelerating healing (see correspondence in the *British Medical Journal*, cited by Sevtitt, Bull, Cruickshank, Jackson, and Lowbury, 1952). This clinical finding is consistent with Lewis's (1927) observation that the triple response elicited by pricking histamine into human skin is also induced by thermal injury, and with the fact that histamine is readily released *in vitro* by heat from the skin of various species of animal (Rosenthal and Minard, 1939). However, in human volunteers given an oral antihistamine immediately after experimental burns were made, Sevtitt *et al.* (1952) could not confirm the clinical findings; and the increased vascular permeability induced by high-temperature burns in rabbits (Weeks and Gunnar, 1949) and by thermal injury in anaesthetized guinea-pigs (Sevtitt, 1949) is not antagonized by high doses of antihistamines. Evidence of this kind from the rabbit and guinea-pig must be given