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FURTHER STUDIES OF THE PSYCHOLOGICAL EFFECTS OF FRENQUEL AND A CRITICAL REVIEW OF PREVIOUS REPORTS[1]

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I. Introduction

Interest in Frenquel[3] was considerably stimulated by Fabing's report (2) that this drug effectively "blocked" the psychological effects of LSD-25 and mescaline. Fabing as well as others (3, 5, 6) has since carried out clinical trials with Frenquel on a variety of conditions in which hallucinations or delusional thinking were conspicuous features. These have included acute and chronic schizophrenia, delirium tremens, post-operative confusional states and senile dissociation syndromes. It was apparently assumed that if Frenquel blocked the effects of hallucinogenic drugs, it might be beneficial in other forms of mental disturbance.

The relationship, if any, of the psychological phenomena induced by hallucinogenic drugs to disorders such as schizophrenia is a controversial question which will not be considered at length in this paper. Serious objections have been raised to use of the term "model psychosis" to characterize intoxication with LSD-25 or mescaline. It has been felt that the term itself might be misleading and in any event was not justified by available evidence. However, in the reported studies of the "anti-hallucinatory" effects of Frenquel, it has been tacitly assumed that hallucinations, for example, produced by LSD-25 or occurring in delirium tremens are the same as, or at least are comparable to, the hallucinatory phenommena of schizophrenia or other functional psychoses and might be similarly modified by the drug.

Even at a descriptive level, there is reason to be doubtful about this assumption. In toxic delirium, visual hallucinations are detailed, vivid, often colorful, kaleidoscopic, and variously farcical or frightening in content. These characteristics have, in fact, been used clinically to identify hallucinations of toxic origin. Visual hallucinations in schizophrenics, if one excludes cases complicated by metabolic disturbances such as severe dehydration, infection, etc., are usually vaguely described in terms of detail or color, stereotyped, symbolic, and frequently meaningful as projected fantasies. Auditory hallucinations are observed far more frequently in schizophrenia than visual hallucinations. The latter are of course common in toxic delirium.

Accordingly, the reports that Frenquel, without producing generalized nervous system depression, does in some specific way "block" or "erase" not only the psychic effects of LSD-25 but also delusions and hallucinations in acute schizophrenia have undoubtedly been received with considerable interest, or even surprise, by many psychiatrists.

II. Review of Previous Studies on the Psychological and Therapeutic Effects of Frenquel

The comments and criticisms made in the course of this review are based upon current literature on the methodology of drug evaluation and the author's own trials and errors in this field. A general review of methods of drug study and sources of error in their use has been given in a previous article (1).

Fabing has reported (2, 3) that premedication with Frenquel caused definite blocking of the psychological effects of 100 micrograms of LSD-25 or 0.4 gm. of mescaline sulfate. One hundred mg. of Frenquel given intravenously during the intoxication are said to have produced dramatic relief of LSD-25 effects within 15 minutes and apparently complete recovery within a half hour. The number of volunteer subjects used was small, and while several were unaware of the amount of Frenquel premedication given, the observers were not "blind". They may have been sub-

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[3] Frenquel: Merrell tradename for α-(4-piperidyl) benzhydrol hydrochloride. The Frenquel used in these studies was supplied by the Wm. S. Merrell Co.

ject to the bias of anticipating "blocking" effects. Moreover, subjects can vary widely in the extent of the psychic phenomena occurring or communicated during one LSD-25 trial as opposed to another, and one subject can differ from another in this regard. The small number of subjects and drug trials per subject fails to allow for this possibility. The importance of the personality structure of the subject, of his psychic state at the time the drug is given, and of the experimental setting as parameters conditioning observed drug effects has been previously emphasized (4).

Fabing has also reported (3) impressive results with Frenquel in patients with "schizophrenic reaction patterns," including schizophrenia *per se*, alcoholic psychosis, senile dissociation syndromes and post-operative confusional states. However, double-blind methods, placebo controls, systematic observational methods, or a design which controlled possible intervening variables were apparently not used in these studies.

These same limitations apply in general to the studies on Frenquel carried out by Proctor and Odland (5). However, these authors did report that 16 of 19 cases of delirium tremens showed complete relief of symptoms within 3–4 hours after receiving 20–200 mg. of Frenquel intravenously. In some cases the responses occurred within 30 minutes. These results are suggestive of a therapeutic effect from Frenquel, but unfortunately control cases and double-blind methods were not used.

Rinaldi *et al.* (6) have described a double-blind study of 16 weeks' duration on 39 chronically psychotic patients. The subjects were divided into two groups. One was on Frenquel for the second four-week period; the other, during the third period. The remaining periods were blocked out with Frenquel placebos. An extensive, descriptive psychiatric profile based on clinical observations was completed on each case by the investigators and attendants at the beginning, at the end of the second period, and at the conclusion of the study. Improvement ascribed to Frenquel was noted in 21 cases.

Excellent efforts at control were made in this study. However, rating scales or other efforts at quantification were apparently not used, nor does the report give the particular standards by which improvement was judged. Errors can arise in studies of this design after breaking the double-blind code, at the point of matching the summarized clinical evaluations with drug and placebo periods. The lack of precision in verbal descriptions of behavior is such that subtle degrees of selection, over-emphasis, under-emphasis, or relative weighting of the many aspects of recorded behavior can introduce significant bias.

III. Studies on Frenquel

The clinical trials with Frenquel to be described in this paper are not intended to be a definitive evaluation of the drug. They were actually carried out as exploratory pilot studies. They involved a relatively small number of cases and are by no means free of methodological defect. They would not be reported at this time except for the fact that the findings were remarkably consistent and in striking contrast to previous claims about the effectiveness of Frenquel. While the negative results in schizophrenics were not surprising, the questionable effects of the drug on toxic delirium prompted the author to repeat the experiments on the alleged capacity of Frenquel to block psychic disturbances induced by LSD-25. Here also the findings were very different from those described by Fabing.

A. Studies in schizophrenic patients

1. A double-blind study was carried out on five chronic schizophrenic patients, age 34–41, whose mental state was persistently characterized by delusional preoccupation and auditory hallucinations. Each patient was interviewed independently by two investigators five times each week for four weeks, and observations on his mental state recorded. During this period, starting at different times in each case, another physician introduced a two-week period of Frenquel administration. Each patient received identical placebos when not on the drug. The dose used was 40 mg. q.i.d.

While minor changes in mental state were recorded during the period of study, there was agreement by both observers that these bore no relationship to Frenquel administration. There was no change in the delusions or hallucinations of the patients. While the drugs

were given for a relatively short period of time, the dosage was higher than that reported to have had beneficial effects on such patients.

2. Individual case studies were carried out on 10 chronic schizophrenic patients, age 31–65, who were conspicuous for their delusions, auditory hallucinations, and in one case visual hallucinations. Each patient was seen daily in independent interviews by two psychiatrists. They were given Frenquel in doses of 20 to 80 mg. q.i.d. for periods varying from 10 to 40 days.

In none of the patients so treated, even with the 80-mg. dose, were significant changes noted in delusions, hallucinations, or mental status in general. Observations contributed by nurses and aides failed to reveal any significant changes in ward behavior.

3. Three schizophrenic patients, clinically similar to those treated in the above studies, were given repeated courses of Thorazine, Frenquel, and both drugs combined over a course of four months. Thorazine in doses of 50 to 200 mg. q.i.d. produced characteristic tranquilizing effects, and the hallucinations and delusional preoccupation of the patients, while still present, were less readily elicited in interview and less conspicuous in their ward behavior. The addition of Frenquel in a dose of 40 mg. q.i.d. to the Thorazine medication for periods of 10 to 20 days and its subsequent withdrawal produced no observable effects on their mental states. Frenquel alone when given to the same patients produced no changes in delusions, hallucinations, or general behavior.

4. A schizophrenic patient with incessant auditory hallucinations, which were readily verbalized as well as expressed in his behavior, was studied in an effort to determine what might be achieved with very high doses of Frenquel. He was given 50 mg. q.i.d. for seven days; the dose was then raised to 100 mg. q.i.d. for two days and finally to 200 mg. q.i.d. for three days. He was interviewed several times daily and carefully observed on the ward. He remained as agitated and hallucinated as ever. No sedative or tranquilizing effects could be detected even on the massive dosage of 800 mg. per day.

5. Three schizophrenic patients with auditory hallucinations and one with visual hallucinations were given 200 mg. Frenquel intravenously on repeated occasions without observable effects upon their hallucinations.

B. Studies on toxic delirium

1. Six patients with delirium tremens with characteristic visual hallucinations were treated. They were given 100 to 200 mg. of Frenquel intravenously. The patients were followed carefully, and the point at which hallucinations cleared was noted. In two cases the hallucinations could no longer be elicited four hours after treatment, but in four the hallucinations persisted for another 24 to 36 hours. One must suspect that the first two cases were nearing spontaneous recovery at the time treatment was given.

2. One patient with visual hallucinations associated with Korsakoff's syndrome and another with auditory hallucinations secondary to pathological alcoholic intoxication were not affected by 200 mg. Frenquel intravenously.

C. Studies on the blocking effects of Frenquel in LSD-25 intoxication

Five cooperative, well-integrated, convalescent schizophrenic patients were studied. The subjects were given repeated doses of 100 micrograms LSD-25 following premedication with Fenquel or Frenquel placebos. They were not informed of the drugs being given. The premedication dose of Frenquel varied from 10 to 40 mg. q.i.d. and was given for periods of two to five days. Matching trials with Frenquel placebos were carried out. The content and duration of the LSD-25 intoxications were followed by two observers. No evidence of blocking by Frenquel could be demonstrated.

In another series of experiments, subjects who had developed a characteristic LSD-25 intoxication from 100 micrograms of the drug were alternately given 100 mg. of Frenquel or a comparable volume of saline intravenously. Six trials were carried out in each of the five subjects. There was no evidence that Frenquel in the dose given changed the nature of the LSD-25 intoxication or shortened its duration when the results were compared with the saline controls.

A self-experiment on the effects of Frenquel on mescaline intoxication was carried out by

the author. The subject had ingested varying amounts of mescaline on previous occasions and was familiar with the effects of that drug. Forty mg. of Fenquel q.i.d. were taken for three days before ingesting 0.2 and 0.4 gm. of mescaline sulfate. The intoxications which ensued were identical in all respects to that which had been previously experienced from these doses of mescaline without Frenquel premedication.

Summary

Treatment of schizophrenic patients with oral and intravenous Frenquel failed to confirm claims that this drug has "anti-delusional" or "anti-hallucinatory" effects on such cases. The drug was of no therapeutic value in the patients treated. Even large doses did not modify their behavior or mental symptoms in any consistent way.

A small series of patients with toxic delirium was treated with intravenous Frenquel. No evidence was obtained that the drug has predictable or consistent effects upon the hallucinations or other mental abnormalities associated with such mental disturbances.

Studies on the effects of Frenquel on LSD-25 intoxication in experimental subjects failed to confirm reports that premedication with this drug "blocks" LSD-25 intoxication or that it exerts a specific suppressive effect when given intravenously at the height of the intoxication. In self-experiments with mescaline sulfate, the author found no subjective evidence that premedication with Frenquel modifies the nature or duration of mescaline intoxication.

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