AN INVESTIGATION INTO THE THERAPEUTIC ACTION OF HYDROXYZINE (ATARAX) IN THE TREATMENT OF NERVOUS DISORDERS AND THE CONTROL OF THE TOBACCO-HABIT

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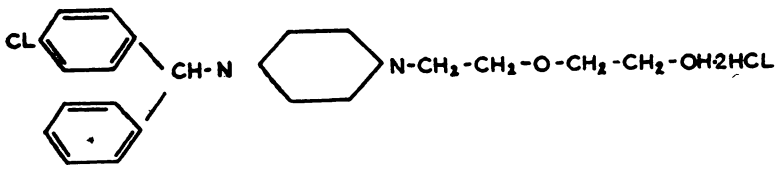
INTRODUCTION

HYDROXYZINE hydrochloride (Atarax, UCB 4492) is a tranquillizer which has attracted much interest in the United States, where it has undergone a series of clinical trials with encouraging results. In order to test the claims of American investigators a trial of hydroxyzine was made on a group of psychotic and psychoneurotic patients in a large mental hospital. The effectiveness of hydroxyzine in controlling the tobacco habit was also tested by using volunteer nurses at the hospital. Their observations provided useful information on the subjective action and side effects of the drug. A small number of young children attending a local child guidance clinic were also included in the clinical trial.

PHARMACOLOGY

Hydroxyzine is described as "a neuroleptic agent" (Delay and Farah), its predominant effect being the relief of nervousness, restlessness, and emotional tension. It is reputed to have no untoward effect on mental performance. Its sedative action differs from that of barbiturates, bromides or chloral hydrate whose quietening effect is the result of hypnosis. Narcolepsy and narcosis do not occur even in doses far in excess of the usual therapeutic range. Its pharmacological action is said to resemble that of chlorpromazine and Pacatal in producing neuro-sedation and muscular relaxation without altering consciousness. Its main value is said to lie in its tranquillizing effect in acute and chronic emotional disturbances of either psychogenic or organic origin.

Hydroxyzine is chemically related to the anti-histaminic group of drugs. It comprises a tertiary ethyl-amine linked to two symmetrical rings. Its special pharmacological properties result from the substantial modifications of its amine group. It has been suggested that hydroxyzine acts by depressing the reticular formation in the brain stem. The structural formula of hydroxyzine is given below:



1-P-Chlorobenzhydryl-4[2-(2-Hydroxyethoxy)-ethyl]-diethylene-diamine dihydrochloride

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THE EXPERIMENT

GROUP I

Clinical Material

The material was selected from several sources. One major group comprised 81 patients drawn from the disturbed wards of the hospital. They were selected almost exclusively for the overactivity or aggressiveness that they exhibited. Most had presented a persistent and difficult nursing problem for a long period. Of this group there were 55 females and 26 males whose ages ranged from 22 to 81. The largest number (43) was made up of schizophrenics with a preponderance of paranoid types. The other selected patients included 15 agitated seniles, 7 aggressive epileptics, 5 cases suffering from mania and 6 from depressive states. A miscellaneous group made up of agitated patients included one patient suffering from Huntington's chorea, one hysteric, one mental defective and two patients suffering from pre-senile dementia.

Clinical Assessment

All patients were observed in their own wards and each was assigned an individual chart on which were recorded daily the number of verbal or physical outbursts. Regular entries were made by either the day or night staff as incidents happened. The nurse in charge in each ward was asked to write a daily report on the behaviour and progress of each patient (and day to day observations were thus obtained). It proved to be a most reliable guide in assessing the patients' response to the experiment and gave a 24-hour record of each patient throughout the trial. Particular emphasis was laid on recording the degree of overactivity, noisiness or submissiveness of each patient as well as of their sociability or withdrawal. Alterations in eating or sleeping habits were also recorded. Undesirable side effects from the drug were also recorded in detail. Each patient was personally interviewed by the same medical observer once a week throughout the trial period. The normal ward routine to which the patients were accustomed was carefully preserved. Routine blood counts and blood pressure recordings were made at weekly intervals.

Administration and Dosage

After a preliminary control period of one week when all sedatives and other tranquillizing drugs were withdrawn, hydroxyzine tablets or placebo tablets, the latter indistinguishable from the former, started to be administered. Each patient received placebo and active preparation alternately and for definite periods, i.e., within the duration of the experiment each patient received the active preparation for a total of 5 weeks with random interspaced periods of 3 weeks during which the inert control preparation was given instead. Both the active and inert preparations were administered in the form of 3 tablets t.d.s. The routine dosage of active tablets was 90 mg. daily. The experiment lasted 8 weeks (during which time each patient was used as his own control). Only the hospital dispenser knew the identity of the active or inert preparations at any given time throughout the trial. After the conclusion of the main experiment on this group a small batch of 12 patients was maintained on a higher dosage of active tablets (270 mg. daily) for a longer period.

Results

The results are summarized in Table I. It was noticed that during the initial stage of the experiment, i.e., during the first two weeks, a number of patients

seemed to improve regardless of whether they were having the active or inert preparation. An unavoidable alteration in their environmental conditions brought about by the very nature of the experiment was thought to be mainly responsible, and it was considered that the patients were responding to the increased attention that their close and continued observation necessitated. This phenomenon has been observed by other workers with controlled experiments (Elkes *et al.*, 1954; Mitchell, 1956).

TABLE I

		Schizophrenics		Senile Psychotics		Epileptics		Manics		Depressives		Miscellaneous	
		M	F	M	F	M	F	M	F	M	F	M	F
Improved	31	7	12	—	7	–	–	2	2	1	–	–	–
Unchanged	43	11	11	–	6	–	4	–	1	–	5	1	4
Worse	7	2	—	–	2	2	1	–	–	–	–	–	–
Total	81	43		15		7		5		6		5	

In assessing results, cases were classified into three categories. In cases labelled "improved", the clinical amelioration was found to be conclusively attributable to the drug. There was a definite improvement in the social behaviour of a number of schizophrenics who became quieter and more responsive. Noisy or aggressive outbursts were greatly diminished. One chronic schizophrenic ceased to be destructive and degraded in habits. Four patients suffering from maniacal overactivity showed considerable reduction of excitability, their lessened psychomotor activity being particularly noticeable. With the switch over to inert medication there was a conspicuous relapse in their symptoms within a week. The restless and purposeless activity of the senile psychotic was successfully controlled in the majority of milder cases, but without effect in the more severe cases. Two cases who had been well controlled by paraldehyde became unmanageable when given hydroxyzine. It should be noted that only one depressive showed signs of improvement—this patient, who suffered from agitated melancholia, was found to be less tense and restless but there was no manifest amelioration in his affective mood. In none of the cases who were found improved was the amelioration more than symptomatic, the structure of their illness remained unchanged and none were sufficiently improved to be discharged from hospital.

The cases described as "unchanged" did not show any significant alteration in their behaviour or symptoms. If any transient improvement took place it could not be ascribed to the effects of the active preparation. This was the case in over half the number of chronic schizophrenics, who seemed totally unaffected, even when a small proportion of them (12 cases) were given a much higher dosage of hydroxyzine (270 mg. daily) after the conclusion of the main experiment. Epileptics and depressive psychotics seemed also in the majority unaffected by the drug. A relatively high proportion of aggressive and excitable epileptics became unmanageable and had to be withdrawn from the experiment because of their violence. In no case was the anti-convulsant medication discontinued during the period of the experiment. Two chronic schizophrenics became markedly more agitated under the influence of hallucinations and showed an accompanying tendency for assaultive or destructive behaviour.

Few side effects were noticed; the one most usually observed by the nursing staff was drowsiness, in approximately 10 per cent. of cases. It was never severe enough to interfere with the patients' daily activity. A very small number of

patients complained of increased intestinal peristalsis and dryness of the mouth. There was no significant lowering of the systolic or diastolic blood pressure in any of the patients during active medication with hydroxyzine. Blood counts showed no variance from the normal.

Group II

This second group comprised 18 patients admitted to the neurosis unit of the hospital. They were selected because they exhibited anxiety symptoms in a clearly recognizable form and were found capable of formulating their subjective experiences adequately with the aid of a questionnaire. The group included 7 anxiety neuroses, 1 obsessive-compulsive state, 6 depressive states and 1 involutional melancholia. The method of administration of the drug and the clinical assessment of results approximated to those used in Group I, the only significant difference being the shorter duration of the trial, which lasted only 4 weeks. Each patient received placebo preparation first for two weeks and then the active preparation 30 mg. t.d.s. for another two weeks. At the end of each placebo and hydroxyzine run they were given a questionnaire in which they were asked to state whether they found the drug beneficial and in what respects their symptoms had been alleviated. Therapeutic interviews were carried out in a routine fashion as with the other patients in the ward.

The results are summarized in Table II and are compiled from both objective and subjective sources, the final assessment being made on the combined observations of medical staff and patients.

Table II

Diagnostic Classification	No.	Improved		Not Improved	
		Male	Female	Male	Female
Anxiety states	7	–	1	3	3
Obsessive compulsive ..	1	–	–	–	1
Depressive states	6	–	1	1	4
Involutional melancholia ..	4	–	1	–	3
Total	18	3		15	

It can be seen that only 3 cases showed signs of improvement. One patient suffering from tension symptoms was much improved and her accessibility to psychotherapy thus enhanced. A recurrent depressive who exhibited severe obsessional symptoms was considerably relieved. The third patient, an involutional melancholic who had failed to respond to electro-convulsive therapy, was significantly improved by the active preparation. The remaining patients were totally unaffected by the drug. Five patients showed drowsiness and one complained of headache and dryness of the mouth whilst receiving the active preparation.

Group III

From the list of cases currently referred to a local child guidance clinic eight children were specially selected because they exhibited anxiety symptoms associated with behaviour disorder. Their ages varied from 8 to 13 years. Five had refused to attend school and attempts to coerce them back into school had regularly precipitated serious temper tantrums, hysterical outbursts or frank panic reactions. Three of them suffered from nausea and vomiting in the morning. All had developed fearful phantasies about their school. A change of

school in two cases had failed to induce them to attend regularly. The remaining three cases were seriously maladjusted children whose overactive behaviour associated with distractibility and tension made them difficult to manage both at home and at school. Two were enuretic, one being also encopretic.

They were each placed on hydroxyzine (10 mg. t.d.s.) for periods varying from three to six weeks. The inactive preparation was not used in view of the limited clinical material and the urgency required in helping some of these cases without incurring possible relapse. It was also felt inadvisable to submit so young a group of patients to full control experiments on an out-patient basis. Both the parents and children were interviewed at weekly intervals at the clinic.

Four of the children who were refusing to attend school showed marked signs of improvement within two to three weeks and began to attend school regularly. There was a significant decrease in their anxiety symptoms and in two cases a complete remission of somatic symptoms. One showed no overt improvement and could not be got back to school. Another relapsed during the next term when hydroxyzine medication was discontinued. The remaining three maladjusted children showed moderate improvement. They were found more manageable at home and were described as less excitable although their basic personality difficulties remained unchanged. Their enuresis or encopresis was likewise unaffected. In two cases the parents had noticed somnolence during certain periods of the day.

GROUP IV

Approximately 50 nurses or their adult relatives who were habitual smokers volunteered to try the efficacy of hydroxyzine in controlling the tobacco habit. The trial extended over a period of 4 weeks which was extended for a further 4 weeks in some cases. Each volunteer took one 10 mg. tablet of hydroxyzine t.d.s., no placebo tablets being used. At the end of the experiment each volunteer received a simple questionnaire which he was asked to complete. Only 23 co-operated finally in both completing the trial and returning the questionnaire. Their ages ranged from 19 to 62 with an average age of 43. The classified results from answers to the questionnaire are summarized as follows:

1. Duration of smoking habit in years:
   Average = 23
   Range = 3–38
   Mode = 25

2. Quantity smoked:
   Average = 21 cigarettes per day
   Range = 8–50 cigarettes per day
   Mode = 20

   (Shag and plug translated into cigarettes)

Cigarettes Per Day	No. of People
8–10	4
11–15	3
20	11
20	3
30	1
50	1

3. Motive for wanting to give up smoking:
   As an experiment = 3
   Health reason = 4
   Expense and health = 16

4. Previous attempt at giving up smoking:
   Yes = 16 No = 7

5. Reason for smoking:
   Pleasure = 17 Habit = 6

6. Effects of giving up smoking:
   Increased appetite = 3
   Need of sweets as substitute = 2
   Substitute not required = 18

7. Effects of hydroxyzine on smoking habit:
   Temporarily helpful = 3
   Made cigarettes taste different = 2
   Craving reduced = 4
   Lessened urge = 4
   No effect = 10

   Total helped to resist = 13
   No pipe smokers in this group

8. No. prepared to continue taking hydroxyzine to curb tobacco habit:
   In favour = 7 Not in favour = 16

9. Tobacco reduced or altogether abolished as result of hydroxyzine trial:
   Ceased smoking = 1
   Reduced amount = 3
   No effect = 19

10. Side effects on taking hydroxyzine:
    No unusual feelings = 7 Unusual feelings = 16
    Feelings or sensations attributable to the effect of the drugs:
    Tiredness = 8
    Feeling of relaxation = 6
    Sleepiness = 1
    Loss of sex urge = 1
    Other sensations mentioned were: stomach pains, excessive urination, coated tongue, headache, giddiness, diarrhoea, fainting and retarded thought.

11. Hydroxyzine helpful in resolving emotional problems:
    No help = 21
    Eased depression = 1
    Relieved pain = 1

Evaluation of the results show that 13 found the drug helpful in resisting smoking at least temporarily whilst 16 record various side effects, particularly tiredness. Only 3 found they had reduced their smoking after the course and only 1 gave it up altogether. With the dosage used there is no relationship between the drug and its effect on smoking with regard to age, duration of smoking habit and the amount of tobacco consumed. Statistically it must be admitted that hydroxyzine has no selective action against the smoking habit. Success or failure in this sphere will always primarily depend on proper motivation, but it does seem that, given the will, hydroxyzine would strengthen the means.

Discussion

An attempt was made to test objectively the efficacy of hydroxyzine as a therapeutic agent in a variety of clinical conditions. The experiment was devised to make three main types of observations irrespective of diagnostic considerations, i.e., to establish whether hydroxyzine successfully relieves tension symptoms, reduces overactivity and aggressiveness and improves social behaviour. The symptomatic response of the patients to the drug was the only criterion used in assessing its usefulness. It was never anticipated that it would

have a specific effect on the intrinsic nature of either psychotic or neurotic illnesses.

The 81 adult psychotic patients selected for the experiment presented a difficult nursing problem because of their chronic overactive behaviour. It was estimated that if their agitation could be appreciably controlled they would become more responsive to the care and guidance of the nursing staff. This was unfortunately not brought about by hydroxyzine in the more severely disturbed psychotics or in the aggressive, overactive seniles. The effects of hydroxyzine were altogether disappointing in chronic schizophrenics, since only 19 out of a total of 43 showed any definite amelioration in their social behaviour. In these there was an increased desire to participate in the activity of the ward and a reduction in the number of noisy or assaultive outbursts. Those cases who were given a much higher dosage (270 mg. daily) in view of their lack of response were not manifestly improved. Hydroxyzine appears to be of definite value in reducing the overactivity of maniacal patients but it was felt that the 90 mg. dose used daily in the experiment was altogether too small to obtain full sedation, a better response was obtained by giving 270 mg. daily. The restlessness and hostility exhibited by some of the senile and epileptic patients were totally unaffected by the current daily doses used. A number of these patients had to be withdrawn from the experiment as they became unmanageable. By contrast the milder form of senile agitation was successfully controlled and the task of the nursing staff considerably eased. The majority of depressive psychotics were not benefited and the anguish of their depressive mood was in no way relieved; in one case however there was a definite improvement in the accompanying agitation.

Of the 18 patients admitted to the neurosis units only one patient out of the 8 selected (on account of their tension symptoms) was manifestly relieved. The serene tension-free effect reputedly produced by the drug and described by American investigators was not observed. The other two improved patients in this group were depressive cases with secondary anxiety features and have already been referred to. The symptomatic response to the drug in the case of neurotic patients was on the whole disappointing.

The results were definitely more promising with children. No categorical opinion is given however since the number investigated was too small and no control groups existed to match the patients' behaviour under placebos. Nevertheless in most of the cases there was a definite lessening of the heightened emotivity and accompanying restlessness which suggests that the excessive reactivity to anxiety-producing situations is successfully neutralized by hydroxyzine. This has been confirmed by Continental investigators (Bayart *et al.*).

Undesirable side-effects and toxic reactions were relatively few and were not noticeably increased with higher dosage. Perhaps significantly the incidence of side-effects was manifestly higher in the sample of normal population used in the smoking experiment and explains perhaps in part why there was a waning of interest for the trial towards the end since only 23 volunteers out of a total of 50 completed it.

The side effects most often referred to in order of their frequency were: tiredness, sleepiness, stomach pain, diarrhoea, giddiness and headaches. Excessive urination, coated tongue, loss of sex urge and retarded thought were other observations made by volunteers in the smoking experiment. No alteration in the blood picture of any patient was ever detected during the trial when routine blood counts were carried out. There was no appreciable change in blood pressure readings made at weekly intervals. No cases of jaundice occurred. All children used in the trial tolerated the drug well.

Summary

The effects of hydroxyzine were assessed by experimental methods on 99 adult patients of a large mental hospital. Out of a total of 81 agitated psychotics only 31 showed signs of improvement in their social behaviour. In a mixed group of 18 neurotics and mild depressives only 3 had their anxiety successfully relieved by the drug. In the case of 8 children attending a child guidance clinic because of anxiety symptoms associated with behaviour disorder, hydroxyzine produced marked improvement in 4 and moderate improvement in 3.

Fifty nurses volunteered to test the efficacy of hydroxyzine in controlling the smoking habit, 23 completed the experiment, 13 found the drug helpful, 16 complained of side effects, only 3 reduced their smoking and one gave it up altogether.

It is difficult to make authoritative claims on the efficacy of hydroxyzine as a therapeutic agent in the treatment of large patient populations when it is realized that only a third of the total adult material utilized made a positive response to the drug. When finally evaluated, results can be summarized as follows:

(*a*) Definitely promising in children because of marked reduction of anxiety.
(*b*) Useful in disturbed seniles (mild cases).
(*c*) Of little value in the restless, aggressive psychotics.
(*d*) Of no manifest benefit in neurotics.
(*e*) Does not demonstrably counteract the smoking habit.

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