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# SIDE EFFECTS OF CHLORPROMAZINE HYDROCHLORIDE

BY

E. M. GLASER AND P. S. B. NEWLING*

*From the Department of Physiology, University of Malaya, Singapore*

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Chlorpromazine hydrochloride (3-chloro-10(3'-dimethylamino-*n*-propyl) phenothiazine hydrochloride) is related to promethazine hydrochloride and to various compounds used in the treatment of Parkinson's disease. It has been claimed to have an analgesic action (Sigwald and Bouttier, 1953 ; Howell, Harth, and Dietrich, 1954), and was shown to prevent vomiting caused by apomorphine (Isaacs and MacArthur, 1955), and in other ways (Moyer, Kent, Knight, Morris, Dizon, Rogers, and Spurr, 1954). Promethazine has a hyoscine-like action (Bain, 1949 ; Glaser, 1953 ; Whittow, 1954), and since this probably plays a part in the treatment of Parkinson's disease and of vomiting, it was of interest to find out whether chlorpromazine exerted a hyoscine-like action on healthy people.

Previous investigators concerned with side effects of drugs have shown that habituation may take place to the taking of tablets and the filling-in of questionnaires (Glaser, 1953 ; Glaser and Whittow, 1953, 1954), and it seemed probable that this habituation had its origin in the cerebral cortex (Glaser and Whittow, 1953). Since chlorpromazine exerts a depressant action on the highest centres of the brain (Sigwald and Bouttier, 1953), it seemed possible that it would inhibit habituation, and the present experiments offered an opportunity to find out whether this was so. (Habituation is taken to mean a gradual diminution of the response to a repeated or continued stimulus, taking place in periods of time of the order of days ; Glaser, 1955.)

## METHODS

The experiments were conducted according to a procedure previously described (Glaser, 1953, 1955) in which all the substances to be tested, as well as an inert substance, are given as indistinguishable tablets at the same time of the day at intervals of 7 days and in a random sequence to all subjects, so that each subject receives every substance and each substance is given to a similar number of subjects each time. The tablets are issued according to a code, and the experimenters do not have the key to this code until the results have been worked out. The subjects of the experiment do not know what substances are to be tested, nor do they know whether the same substance or different substances are given each time. The results are recorded on carefully designed questionnaires about 1½ hr. after the substances have been taken. The validity of this procedure was confirmed in experiments designed to estimate its errors (Glaser, 1954 ; Glaser and Whittow, 1954).

Two experiments were conducted on two different groups of subjects. In one experiment 50 students were given indistinguishable sugar-coated tablets, containing either 25 mg. chlorpromazine hydrochloride or lactose, so that half the subjects took the drug first and half the subjects took the lactose first. In the other experiment 80 students were given 50 mg. chlorpromazine hydrochloride, 25 mg. chlorpromazine hydrochloride, 0.75 mg. hyoscine hydrobromide or a lactose dummy in sugar-coated tablets, as described above, so that each kind of tablet was preceded by every other kind of tablet in an equal number of tests. There was no obvious self-selection among the subjects, since the number of students who were able to volunteer for the experiment but did not do so was less than 5%. The questionnaires were similar to those previously described (Glaser, 1953 ; Glaser and Whittow, 1954), but the subjects were also asked to record their pulse rates and, in the experiment on 50 subjects, to record their own mouth temperatures with numbered thermometers, which they placed in their mouths simultaneously for 3 min. The thermometers were then collected and the readings which had been recorded were checked.

Associations between the incidence of various symptoms were calculated by 2 × 2 tables using the $\chi^2$ method and applying Yates's correction for continuity, while the significance of differences between pulse rates was assessed by means of Student's $t$ test.

## RESULTS

In the experiment in which 25 mg. chlorpromazine hydrochloride was compared with a dummy tablet the only significant difference was that chlorpromazine was considered unpleasant by 11 subjects and the dummy by 3 ($\chi^2=4.070$, $P<.05$). The mean pulse rate was 85 after taking chlorpromazine and 81 after taking the dummy ($.05>P>.02$), but the mouth temperatures were the same.

* Medical Research Council Scientific Staff.

The results of the experiment in which 80 subjects were given in turn a dummy substance, 25 mg. chlorpromazine, 50 mg. chlorpromazine, and 0.75 mg. hyoscine are shown in Table I. The statistical significance of the results is shown in Table II. The number of subjects who took each drug varied, because some students missed certain classes and therefore missed taking certain drugs, but the proportion of absentees was never more than 5%,

TABLE I

EFFECTS OF VARYING DOSES OF CHLORPROMAZINE HYDROCHLORIDE, COMPARED WITH THE EFFECTS OF HYOSCINE HYDROBROMIDE AND A DUMMY TABLET

| Symptom | Dummy | Chlorpromazine | | Hyoscine 0·75 mg. |
|---|---|---|---|---|
| | | 25 mg. | 50 mg. | |
| Headache | 18 | 15 | 19 | 28 |
| Sleepiness | 23 | 31 | 50 | 54 |
| Tiredness | 20 | 29 | 44 | 43 |
| Flushing of face | 12 | 11 | 13 | 19 |
| Nausea | 12 | 12 | 27 | 36 |
| Inability to think clearly | 9 | 12 | 20 | 34 |
| Dryness of mouth | 30 | 47 | 51 | 62 |
| Backache | 10 | 10 | 18 | 14 |
| Giddiness | 15 | 10 | 27 | 47 |
| Faintness | 5 | 4 | 15 | 29 |
| Feeling unwell | 5 | 9 | 23 | 28 |
| Hunger | 19 | 24 | 21 | 22 |
| No. of symptoms recorded by all subjects | 178 | 214 | 328 | 416 |
| No. of subjects showing any effect | 62 | 58 | 70 | 71 |
| Substance considered pleasant | 7 | 3 | 6 | 4 |
| Substance considered unpleasant | 12 | 22 | 32 | 45 |
| Mean pulse rate | 81 | 81 | 90 | 76 |
| No. of subjects taking tablet | 78 | 76 | 76 | 77 |

and it could not have invalidated the results. Chlorpromazine (25 mg.) again produced results which did not differ much from those obtained with the dummy, except that in this group of subjects dryness of the mouth was significantly more frequent after the chlorpromazine than after the dummy, and the number of subjects who considered 25 mg. chlorpromazine unpleasant was not significantly greater than the number who considered the dummy unpleasant ($\chi^2=3.365$, $.10>P>.05$). Both 50 mg. chlorpromazine and 0.75 mg. hyoscine produced significantly more symptoms than did either 25 mg. chlorpromazine or the dummy. The incidence of symptoms was somewhat higher after hyoscine than after 50 mg. chlorpromazine, but only inability to think clearly, faintness, and giddiness were significantly more frequent after hyoscine than after 50 mg. chlorpromazine. The total number of symptoms recorded by all subjects, however, was also signifi-

TABLE II

STATISTICAL SIGNIFICANCE OF DIFFERENCES GIVEN IN TABLE I

Only significant differences are shown ($P<.05$). Highly significant differences ($P<.01$) are marked *

| Substances Compared | Symptom | $\chi^2$ |
|---|---|---|
| Chlorpromazine 25 mg. —lactose dummy | Dryness of mouth | 7·508* |
| Chlorpromazine 50 mg. —lactose dummy | Sleepiness | 18·916* |
| | Tiredness | 15·187* |
| | Nausea | 7·227* |
| | Inability to think clearly | 4·575 |
| | Dryness of mouth | 11·544* |
| | Giddiness | 4·833 |
| | Faintness | 4·928 |
| | Feeling unwell | 13·163* |
| | Substance considered unpleasant | 12·190* |
| Hyoscine—lactose dummy | Sleepiness | 24·003* |
| | Tiredness | 13·427* |
| | Nausea | 16·398* |
| | Inability to think clearly | 18·970* |
| | Dryness of mouth | 26·694* |
| | Giddiness | 26·505* |
| | Faintness | 20·314* |
| | Feeling unwell | 18·997* |
| | Substance considered unpleasant | 29·072* |
| | Number of subjects showing effect | 4·156 |
| Chlorpromazine 50 mg. | Sleepiness | 8·563* |
| ,, 25 mg. | Tiredness | 5·166 |
| | Nausea | 6·760 |
| | Giddiness | 9·145* |
| | Faintness | 6·015 |
| | Feeling unwell | 6·690* |
| | Number of subjects showing effect | 5·986 |
| Hyoscine—chlorpromazine 25 mg. | Headache | 4·443 |
| | Sleepiness | 12·173* |
| | Tiredness | 4·119 |
| | Nausea | 15·624* |
| | Inability to think clearly | 13·319* |
| | Dryness of mouth | 5·633 |
| | Giddiness | 35·492* |
| | Faintness | 21·857* |
| | Feeling unwell | 11·242* |
| | Substance considered unpleasant | 12·346* |
| | Number of subjects showing effect | 6·152 |
| Hyoscine—chlorpromazine 50 mg. | Inability to think clearly | 4·578 |
| | Giddiness | 8·973* |
| | Faintness | 5·156 |

cantly higher after hyoscine than after chlorpromazine ($\chi^2=14.723$ ; $P<.01$). The mean pulse rate in this group of subjects was the same after 25 mg. chlorpromazine and after the dummy, but it was significantly higher after 50 mg. chlorpromazine than after the dummy ($t=3.6443$ ; $P<.01$), and it was significantly lower after 0.75 mg. hyoscine hydrobromide than after the dummy ($t=3.2036$ ; $P<.01$).

Fig. 1 shows the frequency distribution of symptoms after each of the four tablets given to 80 subjects. Although the distribution was not binomial, it is evident that the response to 25 mg. chlorpromazine closely resembled the result obtained with the dummy, while the response to 50 mg. chlorpromazine closely resembled that

with hyoscine. This further confirms the results given above.

Further analysis of the results showed that certain subjects who had reported symptoms of one kind or another had answered the question whether they felt unwell in the negative. Fig. 2 compares the number of symptoms recorded by these subjects with those recorded by subjects who considered themselves to be unwell (irrespective of substances taken), and it shows that those who thought that they were unwell recorded more symptoms (mean 8.71) than those who thought that they were well (mean 2.73). Since the relative incidence of symptoms after taking each substance was the same, whether the subjects considered themselves well or unwell, this does not affect the above conclusions, but it suggests that the subjects fell into two distinct groups with regard to the number of symptoms they reported, and that those who tended to report more symptoms could be picked out by a tendency to consider themselves unwell. This opens up possibilities for research on individual susceptibilities.

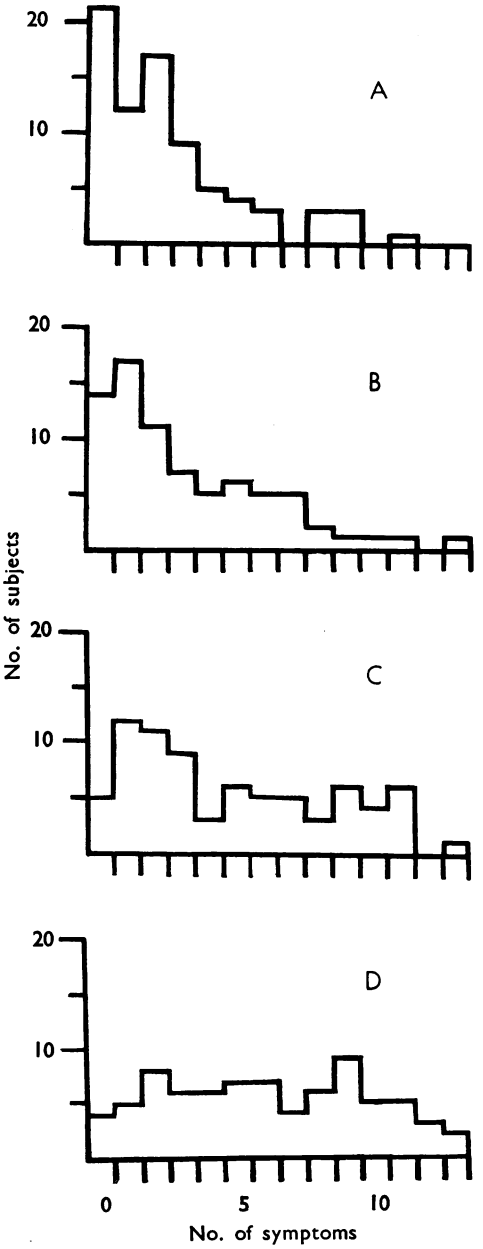


FIG. 1.—Frequency distributions of the number of symptoms reported after taking a dummy tablet (A), chlorpromazine hydrochloride (B, 25 mg., and C, 50 mg.) and hyoscine hydrobromide (D, 0·75 mg.). Number of subjects, 80.

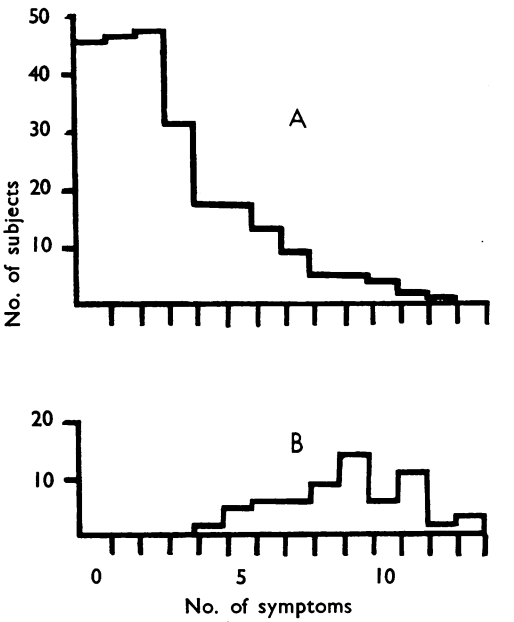


FIG. 2.—Frequency distribution of the total number of symptoms recorded by subjects who considered themselves to be well and subjects who considered themselves to be unwell. A, well; B, unwell. Number of subjects, 80.

Comparison of the results obtained with 0.75 mg. hyoscine hydrobromide in the present experiment (Table I) and with 1 mg. of the same drug in a similar experiment (Glaser, 1953, Table I) showed that the differences between the effects of both doses were compatible with random differences between two identical samples. This conforms with previous findings at sea in which no significant difference was found between the effects of 0.6 and 1.2 mg. hyoscine hydrobromide (Holling,

McArdle, and Trotter, 1944), and it suggests that the optimal dose of this drug is about 0.6–0.75 mg.

*Habituation.*—Seven days after the cross-over experiment with 4 tablets, each subject was given the same type of tablet as he had received on the first day of the experiment, while all other procedures remained unchanged. Only 62 of the subjects were available to repeat the first test and their responses at the beginning and end of the experiment are compared in Tables III and IV.

TABLE III
SYMPTOMS RECORDED AFTER GIVING THE SAME SUBSTANCES TO THE SAME SUBJECTS IN DIFFERENT TESTS
(62 subjects)
Where the difference is significant, the numbers are underlined

| Symptom | No. of Subjects Showing Symptom | |
|---|---|---|
| | 1st Test | 5th Test |
| Headache | 25 | 15 |
| Sleepiness | 38 | 34 |
| Tiredness | 36 | 31 |
| Flushing of face | 15 | 8 |
| Nausea | 23 | 18 |
| Inability to think clearly | 18 | 16 |
| Dryness of mouth | 41 | 34 |
| Backache | 10 | 8 |
| Giddiness | 35 | 18 |
| Faintness | 15 | 12 |
| Hunger | 15 | 12 |
| No. of symptoms | 271 | 206 |
| Substance considered unpleasant | 31 | 26 |

TABLE IV
EFFECTS OF GIVING THE SAME SUBSTANCE TO THE SAME SUBJECTS IN DIFFERENT TESTS

| Substance | No. taking Substance | Total No. of Symptoms | | $\chi^2$ | P |
|---|---|---|---|---|---|
| | | 1st Test | 5th Test | | |
| Lactose dummy | 15 | 49 | 28 | 6·775 | 0·01 |
| Chlorpromazine, 25 mg. | 14 | 49 | 31 | 4·820 | 0·02–0·05 |
| Hyoscine | 15 | 96 | 77 | 3·936 | 0·05 |
| Chlorpromazine, 50 mg. | 18 | 77 | 70 | 0·389 | 0·50–0·70 |

All symptoms were less frequent when substances were given for the second time than when they were given for the first time, but giddiness was the only symptom which decreased significantly ($\chi^2=8.443$; $P<.01$), while the decrease in the incidence of headaches was approaching statistical significance ($\chi^2=3.642$; $P<.05$). The total number of symptoms recorded by all subjects, however, decreased by a highly significant amount ($\chi^2=13.204$; $P<.01$). Table IV shows that this decreased incidence of symptoms was unevenly distributed among the various substances. The decrease in the total number of symptoms recorded after the dummy for the second time amounted to 42%, and it was highly significant, whereas the decrease in the number of symptoms after 25 mg. chlorpromazine was only slightly smaller. The decrease after hyoscine hydrobromide was only just significant. After 50 mg. chlorpromazine, however, the decrease of symptoms between the first and the fifth day of the experiment was insignificant. This suggests that habituation to the experiment had taken place, but that this habituation was inhibited by 50 mg. chlorpromazine.

## DISCUSSION

It seems evident from the above results that 50 mg. chlorpromazine has an action which resembles that of 0.75 mg. hyoscine hydrobromide, but chlorpromazine accelerates the heart rate, whereas hyoscine slows it. Chlorpromazine in doses of 50 mg. must also have some action on the cerebral cortex, since it clearly inhibited habituation to the experiment, and this conforms with reports of its value in the treatment of psychiatric conditions and in anaesthesia. Twenty-five mg. of chlorpromazine has very little effect on healthy people, but it is not entirely inert when compared with lactose.

Previous experiments have shown that drugs which have a hyoscine-like central action on dry land are effective in the prevention and treatment of motion sickness (Glaser, 1953, 1955), and it has been suggested that side effects of drugs may give some indication of their effectiveness against motion sickness (Whittow, 1954). The present results suggest, therefore, that 50 mg. chlorpromazine might be a useful preventive for motion sickness. The findings of Isaacs and MacArthur (1955) that such a dose of chlorpromazine was effective against vomiting induced by emetine are not conclusive, owing to the possibility that the central nervous mechanism of vomiting caused by emetine differs somewhat from that of vomiting in motion sickness (Borison and Wang, 1953). Handford, Cone, Chinn, and Smith (1954) have, in fact, found 50 mg. of chlorpromazine ineffective during prolonged exposures to sea-sickness. The effectiveness of remedies for motion sickness depends, however, to some extent on the kind of motion and on the state of adaptation of the patients (Glaser, 1955), so that it is possible that chlorpromazine might be effective against motion sickness in some circumstances.

The inhibition of habituation by chlorpromazine requires confirmation, but it offers some hope that chlorpromazine may provide a tool for the study of the physiological basis of this phenomenon.

## SUMMARY

1. Twenty-five mg. chlorpromazine had little effect on healthy people.

2. Fifty mg. chlorpromazine produced effects similar to those of hyoscine, including sleepiness, tiredness, and dryness of the mouth, but it increased the pulse rate.

3. There was some evidence that 50 mg. chlorpromazine inhibited habituation to experimental procedures, and this indicates a depressant action on the cerebral cortex.

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