EFFECT OF CHLORPROMAZINE ON THE FUNCTION OF THE ENDOCRINE ORGANS

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We have heard of many reports on the action of chlorpromazine to date, but informations on many points concerning its influence on the system of endocrine organs are too meagre as yet. In the following paper, the authors will report on the results of their study on the effect of the drug on the said system.

EXPERIMENTAL SUBJECTS AND METHOD

In the period of 7 months from June to December 1955, we administered chlorpromazine to 3 cases each of women in the early and the later stages of pregnancy and suffering from toxemia of late pregnancy, and 2 cases of postclimacteric women, 11 cases in total, and examined the change of their hormone values following the administration.

The gonadotropin in their urine was extracted by adsorbing with kaolin (Bradbury et al., 1949), and immature rats 21 days after birth, divided into groups of 4 each, were intraperitoneally injected with the extract once a day for 3 days and were sacrificed on the 4th day to weigh their ovaries. The results were compared with the weight of rats’ ovaries following intraperitoneal injection of Anteron (product of Schering, Germany) and expressed in Anteron units. Urinary estrogen was measured by Jayle’s method (1952), used in combination with Stimmel’s chromatographic method (1946). Urinary pregnanediol was extracted by Mack et al.’s method (1949), concentrate sulfuric acid was added to it for coloration and was subjected to colorimetric analysis at 430 mμ, using a Hitachi spectro-photoelectric colorimeter. Urinary total 17-hydroxycorticoid was determined by Reddy’s method (1952) and urinary total 17-ketosteroid by Drekter’s method (1947). For Friedmann’s tests, rabbits of 2,000-2,300 g in weight were used after trial laparotomy for assuring their normality.

Chlorpromazine was administered by intramuscular injection in one dosis of 25 mg on the first day and from the 2nd through 5th days in 2 doses of 25 mg each per woman daily, so that the total quantity applied to each woman came up to 225 mg.

EXPERIMENTAL RESULTS

The change in the mean excretion of gonadotropin following intramuscular injection of chlorpromazine was as shown in Fig. 1, which shows that the excretion of gonadotropin was frankly reduced in every case.

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Fig. 1. The Change in the Mean Excretion Value of Gonadotropin Following Chlorpromazine Injection

Fig. 2. The Change in the Mean Value of Excretion of Estrogen under Chlorpromazine

in similar cases is illustrated in Fig. 2. In non-gravida and in the cases of early stage of pregnancy, in whom the estrone value is higher than the other estrogen values, the former is seen more perceptibly reduced, while in the cases of late pregnancy, where the estriol value is high, this value is subject to marked reduction.

The same change of total 17-hydroxycorticoid, of pregnanediol and of total 17-ketosteroid is given in Fig. 3. The two former were always perceptibly reduced, but the last showed little change following chlorpromazine administration.

Fig. 4 illustrates how the excretion of 17-hydroxycorticoid following administration of ACTH is affected by injection of chlorpromazine. 40 units of ACTH (Armour)
were dissolved in 500 ml of 5 per cent glucose solution and administered by intra-venous drop injection in 4 hrs. The quantity of excreted 17-hydroxycorticoid was measured on the day before, one day and two days after the beginning of drop injection. The mean values of the females in menopause to whom ACTH only was administered are given in the upper and those of 2 women in menopause to whom ACTH and chlorpromazine were given in combination are shown in the lower part of the figure. It is seen that administration of ACTH alone causes an obvious rise of 17-hydroxycorticoid value but chlorpromazine inhibits the rise.

In Fig. 5 is illustrated the effect of chlorpromazine on the results of Fried-
Fig. 4. The Excretion of 17-Hydroxycorticoid Following Administration of ACTH and that Affected by Injection of Chlorpromazine

Results of Friedman's test

<table>
<thead>
<tr>
<th>Number of the group</th>
<th>Intramuscular injection of chlorpromazine</th>
<th>Intravenous injection of 10 units of Physex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25mg of chlorpromazine as one dose</td>
<td>ACTH administration by intravenous drop injection</td>
</tr>
<tr>
<td>2</td>
<td>5mg</td>
<td>(positive)</td>
</tr>
<tr>
<td>3</td>
<td>10mg</td>
<td>(negative)</td>
</tr>
<tr>
<td>4</td>
<td>20mg</td>
<td>(negative)</td>
</tr>
</tbody>
</table>

Fig. 5. The Effect of Chlorpromazine on the Results of Friedman's Tests
man's tests. 10 Units of Physex Leo (a chorionic gonadotropin preparation), when injected into the auricular vein of rabbits, causes their reaction in Friedman's tests to turn positive. If such rabbits are intramuscularly injected with 5 mg, 10 mg or 20 mg of chlorpromazine one hr. before and 5 and 11 hrs. after the Physex injection, the reaction turns negative in the cases injected with doses of 10 mg each or more. This shows that chlorpromazine inhibits Friedman's reaction.

DISCUSSION

Administration of chlorpromazine causes reduction of the values of excreted gonadotropin, estrone, estradiol, estriol, pregnanediol, and total 17-hydroxycorticoid, but the total 17-ketosteroid value is little affected thereby, in pregnant, toxemic and postclimacteric women. The reduction of the secretion of hormones is strong in the cases of those in stimulated secretion and weak in the cases of those depressed in secretion.

Chlorpromazine suppresses the excretion of gonadotropin not only in non-gravid postclimacteric women, but also in pregnant women. This suggests that chlorpromazine inhibits the secretion of chorionic gonadotropin too, beside pituitary gonadotropin.

After that nervous anesthesia is induced by artificial hibernation, the response to coldness often observed in the system of pituitary-thyroid-adrenal glands is said to be eliminated (Cahn et al., 1953), but Cheynol (1954) has reported that even when chlorpromazine is applied to animals with extirpated pituitary gland, the ascorbic acid in the adrenal diminishes with a rise in the quantity of ACTH administered.

According to our measurements, the 17-hydroxycorticoid value decreased following administration of chlorpromazine. The cause of this is of course found in the main in the inhibitory effect of this drug on the center of internal secretion, but from the action of chlorpromazine in restraining the effect of ACTH in expediting the secretion of adrenocortical hormone, it may be inferred that it is also effective in lowering the endocrine function of the adrenal cortex, a peripheral endocrine organ.

Krais et al. (1955) say that chlorpromazine causes a stand still in the estrual period of rats, and Kobayashi et al. (1955) and Shibusawa et al. (1955) that it inhibits the function of the hypothalamus and decreases the pituitary gonadotropin.

We have seen that an administration of chlorpromazine reduces the excretion of gonadotropin in urine. On the other hand, the drug inhibits the response of the ovaries to gonadotropin in Friedman's test. Consequently, it is clear that the reduction of the estrogen and the progesterone values is due to central causes as well as reduction in the function of peripheral glands.

SUMMARY

When chlorpromazine is administered to women in both the early and the later stages of normal pregnancy, with toxemia of late pregnancy or in postclima-
macteric age, the excretion into urine of estrone, estradiol, estriol, pregnanediol and total 17-hydroxycorticoid was found reduced, but that of total 17-ketosteroid was little affected.

Following administration of chlorpromazine, the values not only of excreted pituitary but also of chorionic gonadotropin were decreased, the action of ACTH in stimulating the adrenal cortex was lowered and the response to Friedman's test was inhibited. Consequently, it is inferred that chlorpromazine, beside depressing the center of internal secretion, simultaneously reduces the function of the peripheral endocrine organs as well as of the placenta.

REFERENCES