Quantitative Aspects of the Antifibromatogenic Action of Synthetic Desoxycorticosterone Acetate

Alexander Lipschutz, M.D., J. V. Luco, and Juan Zañartu

(From the Department of Experimental Medicine, National Health Service of the Republic of Chile, Santiago, Chile)

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The results of the experiments of Lipschutz and Iglesias (3) and Iglesias (1) showing that abdominal fibroids can be induced in almost every castrated female guinea pig subjected to prolonged treatment with subcutaneous injections of estrogens offered the opportunity to study also the antitumoral action of certain gonadal steroids. Fibroids induced by estrogens were prevented by the simultaneous administration of progesterone (4) or testosterone (9). The most convenient method for such experiments is the implantation of tablets under the skin by the technic of Deanesly and Parkes. The fibromatogenic tablet of estradiol was implanted on one side of the body; a tablet of progesterone was implanted on the other side of the same animal (6). On account of the great similarity between progesterone and desoxycorticosterone as to chemical structure it was thought that this cortical hormone may also have antifibromatogenic activity. This has been proved to be true. In experiments with the simultaneous implantation of tablets of estradiol and desoxycorticosterone acetate (7, 8, 11), this synthetic cortical hormone was found to have great antifibromatogenic activity. Uterine bleeding induced by the estrogen was also prevented by desoxycorticosterone acetate.

When dealing with the comparative antifibromatogenic activities of steroids, quantitative results were expressed as a ratio between the fibromatogenic estrogen and the antifibromatogenic steroid. This ratio was more favorable with desoxycorticosterone acetate than with testosterone propionate (8). The quantity of desoxycorticosterone able to prevent fibroids was only about three times that of the fibromatogenic a-estradiol. But the question arises whether the preventive effect really depends upon a given ratio between the fibromatogenic and the antifibromatogenic steroid, or whether the antifibromatogenic action is governed by other quantitative laws. These quantitative aspects are also of fundamental importance for the whole problem of the antagonism of sex hormones, as was recognized years ago in work with ovarian grafts by Lipschutz and his associates (10).

EXPERIMENTS

Fragments of tablets of a-estradiol and synthetic desoxycorticosterone acetate were implanted under the skin of 42 castrated female guinea pigs. The tablets were prepared by compression. The weight of the fragments used varied greatly. By this means variable ratios between the quantities of absorbed estradiol and absorbed desoxycorticosterone were obtained. The animals were sacrificed 57 to 64 days later. A group of 8 animals into which only tablets of estradiol were implanted served as controls. The results are given in Table I and examples are pictured in Figs. 1-3.

Uterine and extragenital fibroids were produced with as little as 1.8 to 3.3 mgm. of estradiol absorbed in the course of about 2 months. The average tumoral effect was more than class 5 in the control group (Table I, group A) according to our classification (2, 5). It must be emphasized that the result with control animals is not always such a remarkable one; an average of only 3 is sometimes obtained under similar experimental conditions (7).

Uterine fibroids were absent and the extragenital fibrous reaction was markedly reduced when 6 to 8 mgm. of desoxycorticosterone were absorbed simultaneously with the estrogen (Table I, group B). The average tumoral effect was 1 in this group; this average was due to small nodules on the spleen (tumoral seed) and to fibrous peritoneal strands, a reaction which is characteristic of a diminished sensibility for the tumorigenic action of estrogens as shown by Vargas and Lipschutz (12). There was not a single animal with an individual spherical tumor of class 1 (about 1 mm. in diameter).

The preventive action of similar quantities of desoxycorticosterone is still observable when the quantity...
of the fibromatogenic estradiol is considerably raised
(Table I, group C). The ratio between the ab-
sorbed estradiol and the absorbed desoxycorticosterone
dropped in group C to 1:1.3, instead of 1:3 in group
between estradiol and the cortical steroid in group D
was no less than in group C. Notwithstanding that
10 out of 20 animals had individual uterine or extra-
genital tumors of class 1, 3 animals had individual

| Table I: Fifty Castrated Female Guinea Pigs (125 to 610 gm.) with Subcutaneous Tablets of Estradiol and Desoxycorticosterone Acetate |

<table>
<thead>
<tr>
<th>Series XXXI and XXXII</th>
<th>Number of animals</th>
<th>Initial weight of tablets</th>
<th>Quantity absorbed</th>
<th>Ratio of steroids</th>
<th>Tumoral effect</th>
<th>Animals with individual tumors of class I</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 8</td>
<td>7.2</td>
<td>2.2</td>
<td>1.8-3.3</td>
<td>0</td>
<td>5.7</td>
<td>7</td>
</tr>
<tr>
<td>B 8</td>
<td>7.6</td>
<td>2.3</td>
<td>1.6-3.1</td>
<td>6.8</td>
<td>1.3</td>
<td>0</td>
</tr>
<tr>
<td>C 14</td>
<td>24.2</td>
<td>7.8</td>
<td>6.1-7.9</td>
<td>10</td>
<td>1:3</td>
<td>1</td>
</tr>
<tr>
<td>D 20</td>
<td>7.2</td>
<td>2.0</td>
<td>5.8-16</td>
<td>0.8-1.6</td>
<td>1:1.3</td>
<td>0.5</td>
</tr>
</tbody>
</table>

1 Belonging to a series of Netter (11).
2 Figures calculated for the free steroid.
3 Figures in parentheses give range.
4 Figures in parentheses indicate tumors transitional between 0.5 and 1.
5 Spherical tumors of 1 mm. in diameter.
6 According to our system of classification (2, 5).
7 B: diminution of the ratio had consequently no influence on the result.
8 In group D the same quantity of estrogen was absorbed as in group B but the quantity of desoxycorticosterone was diminished below a total of 6 mgm. absorbed in the course of 2 months. The average ratio extragenital tumors, in animals of group D. Absorption of (from a pellet of 7.6 mgm. of the acetate) in 57 days. Ratio, 1.24. Total tumoral effect, 3.5. Series XXXII. 38.

B, of the fibromatogenic estradiol is considerably raised (Table I, group C). The ratio between the absorbed estradiol and the absorbed desoxycorticosterone dropped in group C to 1:1.3, instead of 1:3 in group between estradiol and the cortical steroid in group D was no less than in group C. Notwithstanding that 10 out of 20 animals had individual uterine or extra-genital tumors of class 1, 3 animals had individual tumors intermediate between 0.5 and 1. The average tumoral effect in group D was considerably greater than in groups B and C. Uterine fibroids, especially extragenital ones, were observable in group D even when the ratio between estradiol and desoxycorticosterone was as high as 1:2.
DISCUSSION

When comparing the results in group D with those in group C (Table I) one may conclude that the same ratio which at higher levels of the fibromatogenic and antifibromatogenic steroids prevents fibroids (group C) may lose this preventive action at lower levels of these steroids (group D). But the following objection can be raised against this conclusion. In experiments in which sufficiently small quantities of desoxycorticosterone acetate were implanted (Table I, group D), absorption proceeded very far in the course of 2 months; in only 8 out of 20 animals were 1.3 to 2.5 mgm. of desoxycorticosterone acetate recovered at necropsy. In the remaining 12 animals of this group absorption was complete or almost complete, the quantities recovered at necropsy being nil or no more than 1 mgm. One might then assume that tumors developed in group D because the pellets had diminished appreciably long before the animals were sacrificed and that for a time sufficient for production of tumors the ratio was below that which was active in group C. This possibility cannot be denied. But this would apply only to a restricted number of cases because only 7 out of the 12 animals mentioned with complete or almost complete exhaustion of the antifibromatogenic steroid corresponded with those animals of group D which had fibroids of class 1 (Table I, last column).

A summary of our results is presented in Fig. 4 in which the quantities of desoxycorticosterone absorbed per day in the above 42 experiments (groups B to D) are given as ordinates against the absorbed quantities of estradiol on the abscissa. The figures of absorption per day, however, are not quite exact; absorption per day diminishes with time when the surface of the pellet has diminished, as shown by different workers. This refers to both steroids, fibromatogenic and antifibromatogenic. Also, as already pointed out, in a number of experiments with tumors the objection is valid that absorption was completed or nearly completed before necropsy (see dot beneath the signs in Fig. 4).

In Fig. 4, the straight diagonal line ab indicates quantities of desoxycorticosterone equimolecular with those of estradiol (mol. wt. of estradiol, 272; mol. wt. of desoxycorticosterone, 324). Fig. 4 would allow for the assumption that the fibromatogenic action of the estrogen can be inhibited by an equimolecular quantity of desoxycorticosterone but that this equimolecular ratio is antitumorigenic only at high levels of the estrogen because the inhibitory effect of desoxycorticosterone would depend also upon a threshold dosage of this steroid. The threshold dosage would be in our experiments about 90 mgm. per day (the horizontal line $a_d e_l$ in Fig. 4). This corresponds to about 0.2 mgm. of desoxycorticosterone per kg. body weight per day. Approaching this quantity the source, if it is a very small pellet, may become exhausted or almost exhausted prematurely. This invalidates somewhat our statements referring to the threshold dosage.

The danger of dropping below a threshold should be considerable when one tries to maintain it with daily injections instead of using pellets. This may serve as a hint in clinical application.

One may question whether Fig. 4 would allow also for the assumption that the antifibromatogenic effect depends solely upon a given threshold dosage of the antifibromatogenic steroid irrespective of the ratio's being equimolecular or not. Subsequent experiments must decide whether such an assumption would be justified.

SUMMARY AND CONCLUSIONS

When tablets or pellets of estradiol and synthetic desoxycorticosterone acetate are implanted simultaneously under the skin of the female guinea pig, the
fibromatogenic action of the estrogen can be inhibited by equimolecular quantities of the adrenal cortical steroid. This holds only for sufficiently high levels of the fibromatogenic estrogen; at lower levels the equimolecular ratio often loses its inhibitory action and the quantity of the antifibromatogenic steroid necessary to prevent fibroids is then a multiple of the tumorigenic one. This outcome may be explained by the assumption that the inhibitory effect depends also upon a threshold dosage of the antifibromatogenic steroid. Ineffectiveness of very small pellets may depend also on a premature more or less complete absorption of the source of the antifibromatogenic steroid.

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