A THERAPEUTIC TRIAL WITH ETHYL-ESTRENOL IN GERIATRIC PATIENTS

by

J. L. Kalliomäki, A. M. Pirilä and I. Ruikka

Ethylestrenol (Δ4-17α-ethyl-17-hydroxyestrene) has recently been made available by Organon (Oss) for clinical trials as an oral anabolizer. In the pharmacological studies performed by Overbeek et al. (1961) at Organon it has been demonstrated that ethylestrenol has in animal tests a more favourable anabolic/androgenic ratio than such currently employed substances as methyltestosterone (20 times more favourable), ethylnortestosterone (6 times more favourable) and Δ1-methyltestosterone.

In clinical trials so far performed, ethylestrenol was shown to have a marked N-retaining effect; according to recent studies a significant decrease of the total urinary 17-KS-excretion is not produced in male persons treated with ethylestrenol in therapeutic doses; the minimal progestative dose of ethylestrenol was shown to be 1 mg daily (glycogen deposition test of Ferin).

Bodyweight, appetite and psychic tonus were reported to be favourably influenced by the treatment with ethylestrenol.

Organon, Oss, kindly supplied us with this new oral anabolizer for clinical trials. The work has been performed in the Municipal Geriatric Home of Turku (Finland) and the results of our observations are presented in this paper.

Material and Methods

Our whole series comprised 51 co-operative patients (17 men, 34 women; aged 61-93 years) in the Geriatric Home. The patients were divided into three groups. The selection was made by lot and during the whole trial neither we nor the test subject knew which treatment each patient was receiving (double-blind technique).

1) Present address: Turku, Linnank. 5 C 51, Finland.
2) Information supplied by N.V. Organon.
The groups were as follows:

**Group 1:** 16 patients (7 men, 9 women), these were given 3 mg of ethylestrenol daily for 8 weeks.

**Group 2:** 17 patients (2 men, 15 women), 1 mg of ethylestrenol daily for 8 weeks.

**Group 3:** 18 patients (8 men, 10 women), lactose-placebo tablets daily for 8 weeks.

The following examinations were made during the test-period and as a control during the week preceding the trial:

*Bodyweight* was determined once before the treatment-period and at the 3rd, 6th and 8th week during the treatment-period.

*Muscle power* of both hands was tested by routine hand-ergometry every second week during the whole test-period.

*A number disc* test (Spoke’s test, modification of Reitan (1957) was performed every second week during the whole test-period. For each test a new disc was used. The test reflects the speed of psychomotoric reactions.

*A subjective evaluation of the psychic status* of the test-subjects was performed daily by the same investigator.

*Serum cholesterol* was determined on the same days that the bodyweight recordings were taken, according to the method described by Pearson *et al.* (1953). *Haemoglobin* determinations (Sahli) were also performed on these days.

*An X-ray examination of left hand* was made before treatment commenced and at the 8th week of the trial. The examinations were performed under standard conditions using a similar middle phalanx from an autopsy as a control. The films were evaluated without the reader’s knowing to which group a subject belonged or which film of a given subject had been taken before the treatment and which at the 8th week.

### Results

**Bodyweight** - The means of the bodyweight determinations in the three groups during the test-period were as follows (kg):

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>3rd week</th>
<th>6th week</th>
<th>8th week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 (3 mg of ethylestrenol)</strong></td>
<td>61.0</td>
<td>62.0</td>
<td>62.2</td>
<td>60.0</td>
</tr>
<tr>
<td><strong>Group 2 (1 mg of ethylestrenol)</strong></td>
<td>58.0</td>
<td>56.5</td>
<td>56.3</td>
<td>56.8</td>
</tr>
<tr>
<td><strong>Group 3 (placebo)</strong></td>
<td>60.6</td>
<td>60.2</td>
<td>60.7</td>
<td>61.4</td>
</tr>
</tbody>
</table>

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It will be seen that in group 1 little increase of bodyweight occurred during the first 6 weeks of the treatment. The mean of this bodyweight increase at the 6th week was 1.09 ± 0.52 kg and it is statistically insignificant ($p > 0.05$). All other changes in the bodyweight, as shown above, are likewise insignificant.

**Muscle power** - The results of the muscle power determinations were as follows:

<table>
<thead>
<tr>
<th></th>
<th>Right hand</th>
<th></th>
<th>Left hand</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of hands tested</td>
<td>Muscle power</td>
<td>No. of hands tested</td>
<td>Muscle power</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incre.</td>
<td>Decr.</td>
<td>No changes</td>
</tr>
<tr>
<td>Group 1</td>
<td>13</td>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Group 2</td>
<td>17</td>
<td>5</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Group 3</td>
<td>16</td>
<td>2</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

In the patients receiving 3 mg of ethylestrenol daily there was an increase in the power of right hand in 46%; in the placebo group this percentage was 12. This difference is significant at the 95% confidence level. All other differences between the test-groups are insignificant. The figures of group 2 (patients received 1 mg of ethylestrenol daily) lie between the figures of group 1 (3 mg of ethylestrenol daily) and group 3 (placebo); this may, we feel, indicate a trend.

**Psychomotoric reaction** - The mean time required by the patients treated with 3 mg of ethylestrenol daily ($n = 10$) for performance of the psychomotoric test used by us was $42 \pm 11.3$ s *shorter* at the 6-8th week of treatment than before the treatment. In group 2 (1 mg of ethylestrenol daily; $n = 13$) this time was $3 \pm 1.7$ s *longer* and in the group 3 (placebo; $n = 9$) $9-15$ s *longer* than before the treatment. The differences between groups 1 and 3 and 1 and 2 are statistically significant ($p < 0.05$). Group 2 did not differ significantly from the placebo-treated group 3.

**Subjective evaluation of the psychic state** - In the first group a psychic stimulation was recorded in 4 cases out of 16, in the second group the figures were 6 out of 17 and in group 3 (placebo) 1 out of 18. These differences are statistically insignificant. In the early stages of treatment with ethylestrenol there was often some tendency to nervousness which disappeared when the therapy had continued for 2 - 3 weeks.

**Serum cholesterol** - Changes in the serum cholesterol levels were as follows (figures are mg%):
Before Treatment-period

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>3rd week</th>
<th>Treatment-period</th>
<th>6th week</th>
<th>8th week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>226</td>
<td>210</td>
<td>227</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>215</td>
<td>187</td>
<td>206</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>221</td>
<td>212</td>
<td>212</td>
<td>220</td>
<td></td>
</tr>
</tbody>
</table>

All changes are statistically insignificant.

*Haemoglobin* did not change significantly over the whole test-period in any of the groups studied.

**X-ray examination of left hand** - Group 1: Before the treatment marked or moderate osteoporosis was seen in 8 cases. After the treatment-period (3 mg of ethylestrenol daily for two months) these osteoporotic changes had become slighter, to judge from their appearance in 5 cases.

Group 2: Marked or moderate osteoporotic changes were seen in 13 cases before treatment; after the treatment (1 mg of ethylestrenol daily for two months) these changes had become slighter in 4 cases.

Group 3: Marked or moderate osteoporosis was seen in 14 cases before the placebo-treatment; after two months "treatment" with placebo osteoporosis had become slighter in 9 cases.

Osteoporotic changes developed or increased during the treatment-period in 5 cases out of 16 treated with 3 mg of ethylestrenol daily, in 4 cases out of 16 treated with 1 mg of ethylestrenol daily and in 5 of 18 cases treated with placebo.

**Side-effects** - In 1 of 9 women treated with 3 mg and in 2 out of 15 women treated with 1 mg of ethylestrenol daily there was a slight and uncertain appearance of masculine-type growth of hair during the treatment.

Gastrointestinal intolerance was not seen in the groups studied during the test-period. Urinary distress developed during the treatment-period in 4 cases out of 33 treated with ethylestrenol (in groups 1 and 2) and in 2 cases out of 18 treated with placebo.

**Discussion**

It is obvious that with 3 mg of ethylestrenol daily it is possible to improve the psychomotoric and muscular performance of geriatric patients. Osteoporotic changes were, however, not influenced by two months of treatment at this dosage level. The results obtained by treatment with 1 mg of ethylestrenol daily did not differ significantly from the results obtained with placebo.

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In evaluation of the slight and uncertain masculine-type growth of hair developed or increased during treatment with ethylestrenol in 3 of 24 women treated one must take into consideration the fact that our patients were very old (aged from 61 to 93 years).

The role of androgens in their endocrine habit is thus primarily great. A very slight addition even of substances with very weak androgen-properties may then, if it is continuous, cause accentuation of androgenic features in their endocrine habits. In our cases this accentuation was so uncertain and slight, however, that it hardly has any clinical importance.

Summary

Some clinical effects of ethylestrenol, an oral anabolizer, have been studied in 33 geriatric patients aged from 61 to 93 years. 16 patients received 3 mg and 17 patients 1 mg daily for two months. The study was performed using double-blind technique and the placebo-treated group consisted of 18 patients.

In the patients treated with 3 mg of ethylestrenol daily a significant improvement was observed in psychomotoric reactions and muscle power. A statistically insignificant weight gain was observed during the first 6 weeks of the treatment although none of the patients was actually underweight. By the 8th week this increase disappeared. Effects of this dose on the serum cholesterol, haemoglobin and osteoporosis did not differ significantly from the results obtained in the placebo group.

The positive results obtained with 1 mg of ethylestrenol daily did not differ significantly from the placebo results.

A slight and uncertain appearance of a masculine-type growth of hair was observed in 3 out of 24 women treated with ethylestrenol.

Gastrointestinal or urogenital side-effects were not seen during the treatment with ethylestrenol.

REFERENCES

DISCUSSION

Tausk: Thank you Prof. Kalliomäki for the interesting data. This paper is now open for discussion.

Houtsmuller: Firstly, can you tell me the mean age of the different groups and secondly can you give me data about the - at least for me - paradoxical difference between the normal cholesterol values and the age. Your results give rather low values. Cholesterol levels recorded in our clinic for this age are very much higher. Perhaps there is a difference in technique. Perhaps there could be a difference also in the normal range compared to our results and perhaps also between men and women in the main cholesterol levels?

Finally: have you some patients with latent diabetes in your groups who did improve in cholesterol- or carbohydrate metabolism, or have you not seen that? Often they can only be detected with a glucose tolerance test.

Kalliomäki: Diabetics were not included in this series. The mean age of the three groups was similar and the cholesterol levels of these patients were between normal limits in this geriatric hospital. The values are slightly lower than normal in Finland but we could not change the technique during this trial.

Bierich: Can your low cholesterol level be explained by differences in nutrition? Can it be for example that nutrition is different in Finland? I suppose that there are differences between here in Holland and Finland.

Dardenne: Which cholesterol did you determine: the combined or the free cholesterol?

Kalliomäki: This is total cholesterol.

Dardenne: In Bonn we have about the same levels for this age, not much higher.

Kopera: I would like to add one thing to the lecture of Prof. Kalliomäki. We now have data on about 530 patients treated with ethylestrenol and the mean dosage applied was higher than the one you used, i.e. the patients received a dose from 2 - 6 mg/day. We have to admit that none of the groups of these patients reported upon include patients of an age-range comparable to your groups, and we do not have any special experience in geriatric patients. Nevertheless I should like to stress the point that among these 530 patients there were only one or two cases with very questionable virilizing side-effects. So it looks very likely to me that the age of the patients and their endocrine situation may be responsible for the virilizing effects that you have seen.

Kalliomäki: I am sure of that.

Kopera: At least in non-geriatric patients one must not expect any virilizing effect even in a dosage which is definitely higher than the one you have used.

Anderson: Is it not possible that this sensitivity to the anabolic steroids both in infancy and old age is related, as Dr Kopera has said, to the endocrine status of these
patients and that these patients do not produce androgens in childhood and in old age have lost their androgens. They do not produce endogenous androgens and are maybe therefore more sensitive to the androgenic effect of anabolic compounds. There are similar examples in endocrinology e.g. when Doca is given to a normal person, hypertension and oedema are readily produced whereas when it is given to a patient with Addison's disease in a dosage which is a little bit too high, such symptoms will develop.

*Tausk:* I think this is what Prof. Kalliomäki has already suggested in his own lecture. Prof. Kalliomäki, do you have any remarks to add to what Dr Anderson has said?

*Kalliomäki:* No, I agree. There seem to be different ideal ratios for anabolic steroids. One is ideal for premature babies, one is ideal for infancy, one is ideal for adults, and one for geriatric patients; it is a function of age.

*Kopera:* I think it is quite clearly seen from Prof. Kalliomäki's interesting data that normal-weight patients would not gain weight when treated with anabolic steroids, regardless how high the dosage used may be. This I believe corresponds very well to all other experiments we have heard of.

*IJzerman:* We have seen in Dr van Wayjen's balance studies that there are patients who loose weight although they have a positive nitrogen balance.

*Overbeek:* I think this is one of the very few examples where data became available on muscular performance and on the psychomotoric test. I wonder if someone else has some data on that? It is very rare indeed and I was very glad to hear Prof. Kalliomäki give us this information.

*Hortling:* I have also made some trials on muscular performance in patients treated with ethylestrenol. In some of the patients who showed a clinical improvement there was an increase of the muscular power. Prof. Kalliomäki's results were very impressive.

*IJzerman:* Prof. Kalliomäki, do you know from your own experience or from literature on this subject of any studies with other anabolic steroids on psychomotoric effects and muscle power?

*Kalliomäki:* I have never heard of any.

*IJzerman:* So you cannot compare it with anything else?

*Kopera:* Except with the results you obtained with Deca-Durabolin.

*Kalliomäki:* Yes, but the results were about the same. We administered 100 mg of Deca-Durabolin in a single dose and we followed the psychomotoric effect and muscular power after it. About two weeks after this injection a marked improvement in psychomotoric reactions was seen but the increase in muscular power was not as pronounced. We presume therefore that a single dose is not enough to improve muscular power. In a few patients there was an almost euphoric effect.

*Van Wayjen:* I would like to ask Prof. Kalliomäki about the food of these patients.
In Finland an investigation on a large scale was done - I think by Ancell Keys - on the serum cholesterol level. Such data are very important in order to evaluate the effects of treatment with anabolic hormones. In the harbours this was higher than in the country. This difference was attributed to a difference in nutrition. More fish is eaten in the harbour areas. So I should like to know whether you have any data about the amount of calories, of protein and fat in the food of your patients?

Kalliomäki: No, we have not. We had difficulties in determining these amounts. We have no exact figures because such geriatric patients are not reliable.

Bierich: I should like to refer to our patients with obesity. As a matter of fact they often have definitely higher levels of cholesterol, being very well nourished, but after three or four weeks of therapy these levels fall. There may be a relationship between these levels and the treatment.

Beck: From my own experience, the cholesterol level varies a great deal in the same patient even when no therapy is given. The evaluation of a cholesterol-decreasing effect of ethylestrenol would appear to require the study of larger groups of treated patients and controls under the same nutritional conditions.

The age and the sex are particularly important. We have observed in a systematic study of 1305 elderly people in the hospiten at Ivry, a gradual decrease of the cholesterol level starting from the age of 70. This applies to every age group but is less marked in women than in men. In the latter the average cholesterol level is 2.48 ± 0.55 g/l between 70 and 74 years and 1.97 ± 0.43 g/l after 90 years.

With regard to my experience with ethylestrenol: a therapeutic study carried out in 25 elderly patients given 0.1 mg/kg/day of ethylestrenol for three months resulted in an average weight gain of 2 kg. The weight gain varies from patient to patient and does not appear to be dependent on the weight before treatment started. The cumulative curve showing the weekly gain does not progress evenly. It usually flattens out at about the third month. This curve is not parallel to the cumulative nitrogen curve. The weight gains seem more associated with the caloric intake than with the retained nitrogen. The mechanism causing the increased food intake under the influence of anabolic steroids is obscure. Ethylestrenol in the given dosage decreased the calciuria in the majority of the patients studied. The study of the calcium balances showed however that the calcium retention remains slight. A calcium retention of the order of 700 mg daily for three months was seen in two cases, the daily calcium intake being 1.5 - 2 g. In these cases the administration of an anabolic steroid only slightly modified the calcium balance.

Tausk: Thank you, Dr Beck. If there are no further questions .... Thank you all for your contributions, the meeting is adjourned.