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PROGESTERONE AND PROGESTATIONAL COMPOUNDS IN THE TREATMENT OF ADVANCED ENDOMETRIAL CARCINOMA

By
Per Bergsjö*

ABSTRACT

Various doses of progesterone in oil and of two progestational compounds (17α-hydroxy-19-nor-progesterone caproate and 17α-hydroxy-progesterone p-butoxyphenyl propionate) have been given to 15 patients with recurrent and/or metastatic endometrial adenocarcinoma and to one patient with metastatic cervical adenocarcinoma, for periods of up to 27 weeks. Regression of lung metastases was noted in 4 of 13 patients, softening of pelvic tumour in 2 of 4, and histological alterations of tumour tissue in 4 of 5 patients. In the patient with metastases from a cervical adenocarcinoma, the disease progressed during the treatment. The significance of the observations is discussed.

The hormonal dependence of carcinoma of the breast and prostate is well established. A logical consequence is to test other suitable tumours for hormonal dependence. In recent years, clinical reports have shown favourable results of progestagens on endometrial carcinoma. Kistner's (1959, 1962) studies indicated that carcinoma in situ of the endometrium might disappear following large doses of progestational compounds. Varga & Henriksen (1961) showed histological changes in endometrial tumour tissue and objective regression in some cases of recurrent disease, treated with 17α-hydroxy-progesterone caproate. Kelley & Baker (1961) and Kennedy (1963) observed objective regression in about one third of the patients with metastatic or recurrent endometrial carcinoma, and Budd Wentz (1964), who administered an oral pro-

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gestagen, saw improvement in almost all patients, both with primary and recurrent disease. Madden (1964) has reported total disappearance of both the primary tumour and the lung metastases in a case of cervical adenocarcinoma treated with a progestational compound.

Since June, 1963, we have treated 15 patients with advanced endometrial and one patient with metastatic cervical adenocarcinoma with progesterone and progestational compounds. This communication deals with the experience gained.

MATERIAL

The diagnosis of the 16 patients at the time of primary treatment is given in Table 1. The primary treatment was surgical in eight and was followed by radiation in four of them. Eight patients had local radium and in two of them this was followed by hysterectomy. The indication for hormonal treatment is given in Table 2. Thirteen patients had lung metastases and 7 local recurrence, alone or combined. In 5 patients tumour tissue was controlled histologically during the treatment period.

The time interval from the primary diagnosis to the finding of the recurrence or the metastases, ranged from one to forty-seven months.

In two patients the hormonal treatment was discontinued after less than four weeks, due to concomitant radiological treatment, which would interfere with the evaluation of the treatment. Both were listed according to the condition at the end of these short periods of treatment.

Table 1.
The localisation of the adenocarcinoma at the time of primary treatment.

<table>
<thead>
<tr>
<th>Localisation</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium only</td>
<td>10 pts.</td>
</tr>
<tr>
<td>Endometrium and endocervix</td>
<td>3 &quot;</td>
</tr>
<tr>
<td>Cervix only</td>
<td>1 pt.</td>
</tr>
<tr>
<td>Endometrium and ovary</td>
<td>1 &quot;</td>
</tr>
<tr>
<td>Endometrium and thyroid</td>
<td>1 &quot;</td>
</tr>
</tbody>
</table>

Table 2.
The indications for progestagen treatment.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung metastases only</td>
<td>9 pts.</td>
</tr>
<tr>
<td>Pelvic recurrence only</td>
<td>3 &quot;</td>
</tr>
<tr>
<td>Lung metastases and pelvic recurrence</td>
<td>4 &quot;</td>
</tr>
</tbody>
</table>

Compounds used

Progesterone in oil, 25 mg per ml, was given to 7 patients, in intramuscular injections. The initial dosage was 200 mg three times weekly, in some cases gradually reduced over a period of months.
17α-hydroxy-19-nor-progesterone caproate, 100 mg per ml, was given to 6 patients, in intramuscular injections. This compound has been shown by Kaiser (1960) to have a progestational action on the human endometrium, and to be about ten times as active as 17α-hydroxy-progesterone caproate. The usual dose given was 100 mg twice weekly. One patient received 100 mg three times weekly with no apparent side effects. 17α-hydroxy-progesterone p-butoxyphenyl-propionate, 200 mg per ml, was given to 5 patients, two of whom had previously received progesterone in oil. This compound has been shown by Diczfalusy (1960) to have about the same effect on the rabbit endometrium as 17α-hydroxy-progesterone caproate. It was given in doses of 200 or 400 mg per week, generally in two injections.

It was intended not to change from one compound to another in the same patient, but this had to be done twice, in order to reduce the number of injections and the quantity of injected material.

RESULTS

Regression or complete disappearance of lung metastases was observed in 4 of 13 patients. The basic data are summarized in Table 3, while the case histories are given below in some detail. In two patients the lung metastases remained stationary, the observation period under progestagen treatment being 16 days in one and 26 weeks in the other. In 7 there was continued growth of lung lesions. The latter 9 plus 3 patients with only local disease in the pelvis are summarized in Tables 4 and 5.

In 2 of the 4 patients with an easily palpable pelvic tumour, there was a definite change in consistency, with softening of the tissue. One of these also showed some regression, with disappearance of easily bleeding excrescences. In both patients there was concomitant change in the histology of the tumours, as shown in Figs. 1–4.

In 4 of the 5 patients in whom tumour tissue was accessible for biopsy, changes were noted during the course of therapy. In one, a second curettage after two months’ therapy was negative for cancer. In the other three, the tumour epithelium showed signs of secretory or acanthomatous conversion (Figs. 1–4).

A comparison of the responding versus the non-responding patients with lung metastases shows no striking difference in mean age of the patients at the time of diagnosis, or in the interval between the initial treatment and the finding of the recurrence. One apparent difference is that the lung metastases in the non-responders were somewhat larger and seemed to grow more quickly than in the responders.

The one patient with lung metastases from a cervical adenocarcinoma showed rapid progression of the lung lesions during the hormonal treatment.

Of the three compounds used, progesterone in oil and 17α-hydroxy-19-nor-progesterone caproate gave favourable response on lung metastases in three
Table 3.
Four patients with favourable effect on lung metastases.
A: Progesterone in oil.
B: 17α-hydroxy-19-nor-progesterone caproate.
C: 17α-hydroxy-progesterone p-butoxyphenyl propionate.

<table>
<thead>
<tr>
<th>Hospital no. Year of birth</th>
<th>Previous treatment and course of endometrial adenocarcinoma</th>
<th>Compound(s) used</th>
<th>Subsequent course</th>
</tr>
</thead>
</table>
Table 4.
Nine patients with no effect of progestagens on lung metastases.
(Abbreviations: see Table 3).

<table>
<thead>
<tr>
<th>Hospital no.</th>
<th>Year of birth</th>
<th>Previous treatment and course of endometrial adenocarcinoma</th>
<th>Compound(s) used</th>
<th>Subsequent course</th>
</tr>
</thead>
</table>
Table 4 (cont.).

<table>
<thead>
<tr>
<th>Hospital no.</th>
<th>Year of birth</th>
<th>Previous treatment and course of endometrial adenocarcinoma</th>
<th>Compound(s) used</th>
<th>Subsequent course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>March 1964: Multiple bilateral lung metastases, and pleural effusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1193/64 M. S.</td>
<td>born 1913</td>
<td>May 1964: Hysterectomy, radium and betatron.</td>
<td>B, 2600 mg/13 weeks</td>
<td>Slight increase in size. Alive and well Sept. 64.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>June 1964: Single density in the left lung.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5.
Three patients with local recurrence only.
(Abbreviations: see Table 3).

<table>
<thead>
<tr>
<th>Hospital no.</th>
<th>Year of birth</th>
<th>Previous treatment and course of endometrial adenocarcinoma</th>
<th>Compound(s) used</th>
<th>Subsequent course</th>
</tr>
</thead>
</table>

of seven cases and in one of six cases, respectively. For both these compounds the histological changes described were demonstrated. Treatment with 17α-hydroxy-progesterone p-butoxyphenyl propionate, on the other hand, did not
Fig. 1.

Fig. 2.
Same patient as Fig. 1, path. specimen no. 1673/64. Biopsy from vaginal recurrence after 12 700 mg progesterone in oil/30 weeks. Adenocarcinoma with signs of acanthomatous conversion. 250 ×.
Patient no. 2347/62, G. B., path. specimen no. 148/64. Biopsy from vaginal recurrence of operated and radiated adenocarcinoma of the corpus and cervix. Poorly differentiated tumour tissue with imperfect acinus formation and papillomatous ingrowth into the lumina. 250 X.

Fig. 3.

Same patient as Fig. 3, path. specimen no. 1102/64. Vaginal biopsy following 17α-hydroxy-19-nor-progesterone caproate: 2400 mg/8 weeks. Several acini are lined by a regular, single cell layer, with cytoplasmic vacuolization. 250 X.

Fig. 4.

419
Patient no. 2512/59. Before the progesterone treatment, the patient has several small round densities in the left lung, one of which is clearly visualized in this frontal view.

give any objective remissions. In one of the three patients who received this compound initially, there was accelerated growth of tumour metastases during treatment, followed by retardation and even slight regression when the compound was discontinued. The case history is given below. In one patient whose lung metastases had disappeared during treatment with progesterone in oil, a lung density reappeared following a change to 17α-hydroxy-progesterone p-butoxyphenyl propionate (Fig. 7). The reason for the change of compound was pain at the injection sites, probably due to oil granulomas. A biopsy from a vaginal recurrence about the same time as the reappearing lung density was noted, showed histologically a more active looking tumour tissue.

The time from the start of hormone therapy until noticeable regression of lung metastases was 2 months or more in the four patients who responded favourably. In the group with continued growth, the lack of effect was generally apparent in less than two months.

Side effects during the course of therapy comprise one case of herpes zoster of the ophthalmic nerve, one case of generalized exanthema, and one case with thoracic and abdominal pain, all transient conditions in spite of continued
Same patient as Fig. 5. After 12,000 mg progesterone in oil/23 weeks, there is complete regression of the lung densities.

therapy. Two patients with favourable effect on lung lesions developed a cough with slight expectoration which may have been due to the therapy. An expected side effect was pain at the site of injection, which developed in two patients after about one year of injections with progesterone in oil, and was most likely due to oil granulomas.

Patients showing regression of lung metastases

Hospital no. 2864/61, M. N., born 1901. An adenocarcinoma of the endometrium was treated with local radium in Dec. 1961, and a subsequent curettage was found to be negative for cancer. In May 1963, the patient had pain in the pelvis, and there was evidence on examination of parametrial spread, the curettage still being negative. At the same time, a small round density was noted in the upper lobe of the right lung, highly suspicious of metastasis. The patient received betatron 31 MV, gamma, 5000 R (Victoreen)/5 weeks, to the pelvis, which resulted in questionable regression of the parametrial thickening. Following this, progesterone in oil was started, 200 mg three times weekly, as the lung density was still present. After one month of hormone therapy, it was almost unchanged, but after two months there was noticeable regres-
Same patient as Figs. 5 and 6. Following 17a-hydroxy-progesterone p-butoxyphenyl propionate, 5200 mg/13 weeks, there is a reappearing density in the same site as that demonstrated in Fig. 5.

Fig. 7.

sion, and after 5 months it could not be seen on the radiographs. During this period, the patient had pain in the pelvis and slight vaginal discharge and bleeding. A curettage in April 1964 showed adenocarcinoma with squamous metaplasia. A change to 17a-hydroxy-progesterone p-butoxyphenyl propionate in May 1964 caused pain at the site of injection. In August 1964 the radiographs of the lungs were still negative, whereas the curettage was still positive for cancer. The parametrial thickening has changed very little during one year of progesterone therapy, and the general condition has been very satisfactory.

Hospital no. 2512/39, A.A.H., born 1895. In 1959 this patient had the uterus and ovaries removed because of an adenocarcinoma of the endometrium with spread to the cervix and the right ovary (histologically proven), and possibly to the peritoneal surface (inspection). Postoperatively she was given radioactive colloidal gold intraperitoneally, and betatron 31 MV, gamma, 3000 R (Victoreen) to the pelvis. One year later, a local recurrence in the vagina was treated with radium. In 1962 there was a new local recurrence in the vagina, and tumour nodules in the bladder. A new operation was performed, with partial resection of the vagina and bladder, removal of the parametrial and pararectal tissue, and of the great omentum. Cancer was found in the resected specimen, and in one node from the omentum. By August 1963, new vaginal metastases had appeared (Fig. 1), and radiographs showed several round densities in the left lung (Fig. 5). Progesterone in oil was then started, 200 mg three times weekly, which caused obvious regression of the local tumour tissue, which also
bled less easily. The lung densities also slowly regressed, and in March 1964 the lungs appeared normal (Fig. 6). A biopsy from the vaginal tumour showed an acanthomatous conversion (Fig. 2). Progesterone in oil, which by this time had been reduced to 100 mg per week, was replaced by 17α-hydroxy-progesterone p-butoxyphenyl propionate, 200 mg twice weekly. Three months later the radiographs were again positive, with a density in the same place as previously (Fig. 7). The vaginal tumour bled more easily and appeared more active microscopically. A short course of 17α-hydroxy-19-nor-progesterone caproate was accompanied by decreased bleeding. The patient was in very good general condition until the autumn of 1964, when uraemia slowly developed. She died in December 1964 after a few weeks in bed. Autopsy was not performed.

_Hospital no. 2360/59, I. O. A., born 1895._ In 1959 and 1960 this patient had a hysterectomy for endometrial adenocarcinoma, and a hemithyroidectomy for an adenocarcinoma of the thyroid, with ingrowth in the trachea. The pathologists considered both tumours to be primary. She was given postoperative radiation to the pelvis and to the neck, and has since been free of recurrence in both locations. In March 1963 multiple round densities in both lungs were discovered, which showed an increase in size until September 1963. At this time progesterone in oil was started, 500 mg per week. Radiographs in November 1963 and in January 1964 showed possible slight regression, and in April 1964 there was obvious regression of bilateral lung metastases. However, after continued therapy, in September 1964 many small densities in both lungs were larger, while some of the previously large nodules could not be found. As the hormone did not appear to affect the majority of metastases, the therapy was discontinued.

_Hospital no. 1909/63, I. J., born 1883._ In August 1963 this patient was treated with radium for adenocarcinoma of the endometrium. Following this, she developed a thrombophlebitis of one leg, an embolus of the right lung, and a cerebral thrombosis. In October 1963 a curettage again showed adenocarcinoma. During this procedure, there was a perforation of the uterus. A radiograph at this time showed a round density in the left lung. She was given 17α-hydroxy-19-nor-progesterone caproate, 100 mg twice weekly, and in January 1964 the density had disappeared. A curettage performed at the same time was negative for cancer. In March 1964, while still on hormone therapy, the patient developed an abdominal tumour which continued to grow until the patient died in July 1964. No autopsy was performed.

_A patient with accelerated tumour growth_

_Hospital no. 535/59, O. N., born 1888._ In 1959 the patient was treated with radium for an adenocarcinoma of the endometrium. In 1962 a local recurrence was found, and she was given betatron, 31 MV, gamma, 2000 R (Victoreen) to the pelvis. Since then she has not presented any signs of local recurrence. In 1962 multiple metastases in both lungs were also found. These had increased in size and number by February 1964, and treatment with 17α-hydroxy-progesterone p-butoxyphenyl propionate was started. She received 200 mg twice weekly. After two months of therapy there was considerable increase in size and number of the lung metastases. In addition, during the two months of treatment, a tumour $8 \times 10$ cm had appeared in the right groin. This was removed, and proved to be adenocarcinoma. The gestagen was discontinued, and after 4 months the condition of the lungs was almost unchanged, with one nodule
apparently even regressing. The patient is still active and seems unaffected by her malignant disease.

DISCUSSION

The disadvantage of using lung metastases as the main criterion for the effect of treatment is that, in most cases, histological proof is not obtained. The four patients in the present material showing response of lung lesions all presented small densities, interpreted as being most likely or almost certainly due to metastases. This interpretation is supported in one case by the reappearance of a lung density following a change in treatment. In another patient endometrial tumour tissue disappeared concomitantly with the lung density. Indirect evidence in favour of a true effect of progestagens on endometrial carcinoma is that in four series of patients a good effect is noted in one third of the patients (Kelley & Baker 1961; Varga & Henriksen 1961; Kennedy 1963; and the present investigator).

The histological examinations during therapy except for one case showed persisting tumour tissue, and in one patient the endometrial tumour even reappeared during the hormone therapy. The histological changes noted, with secretory and acanthomatous conversion, may indicate a further step in tumour differentiation and possibly slower tumour growth. The disappearance of lung densities is likely to be a temporary reversible regression of tumour tissue, as exemplified in the reappearing density in one patient.

In two patients with favourable response on lung densities, pelvic and abdominal tumours continued to grow during treatment. This may be explained by Kennedy's (1963) observation that hormone treatment acts best in areas not previously irradiated. Another factor may be differences in tumour size and differentiation.

Of the three compounds used, progesterone in oil and 17α-hydroxy-19-norprogesterone caproate both produced beneficial effects. 17α-hydroxy-progesterone p-butoxyphenyl propionate, on the other hand, seemed to accelerate tumour growth in two patients, one of whom had previously responded to progesterone in oil, while none of the four patients treated with this compound had any tumour regression. Since this compound differs from that most commonly used in previous trials (17α-hydroxy-progesterone caproate) by the ester only, these observations are rather surprising. It may, of course, be a purely accidental result in a small group of patients, or the dosage may have been inadequate. However, the results with 17α-hydroxy-progesterone p-butoxyphenyl propionate were so disappointing that we refrained from further tests.

Dosage and administration have so far been largely empirical. It seems that very high doses of progesterone and progestagens can be given without any
side effects. In the present material the patients with favourable response were given 200 mg progesterone in oil three times weekly, or 100 mg 17α-hydroxy-19-nor-progesterone caproate twice weekly.

The depot effect of the esters used seems well established (Diczfalusy 1960; Kaiser 1960). To obtain some information about the rate of excretion of the progesterone in oil we collected urine for 8 days from a patient who started treatment with this compound, 200 mg three times weekly, and analyzed the daily excretion of pregnanediol and pregnanetriol*. The result is shown in Fig. 8. It is seen that the pregnanediol excretion increases considerably on the first day of treatment, and is kept at a high, slightly fluctuating level with administration three times per week. Except on the first treatment day, the pregnanetriol excretion lies within the normal range.

![Graph showing daily urinary excretion of pregnanediol and pregnanetriol.](image)

Fig. 8. Patient no. 586/64 G. F. Daily urinary excretion of pregnanediol and pregnanetriol in a patient who received 200 mg progesterone in oil 3 times weekly. Each portion consisted of urine passed from 8 a.m. one day till 8 a.m. the next. The injections were given before noon on the 2nd, 5th and 7th day, the first being a control day before the start of treatment.

* Pregnanediol was determined by the method of Klopper et al. (1955).
Pregnanetriol was determined by the method of Fotherby & Love (1960).
Repeated intramuscular injections over a long period have several disadvantages. If oral progestagens can be shown to have the same effect, these should probably be preferred. The report of Budd Wentz (1964) on oral medication is very encouraging.

ACKNOWLEDGEMENTS

A. B. Leo, Hälsingborg, kindly supplied the 17α-hydroxy-progesterone p-butoxyphenyl propionate.
Nyegaard & Co. A/S, Oslo, kindly supplied the progesterone in oil.
Dr. Tore Sanner, Norsk Hydro's Institute for Cancer Research, Oslo, performed the pregnanediol and pregnanetriol analyses.

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Received on December 21st, 1964.