HORMONAL EFFECTS OF TAMOXIFEN IN OLIGOSPERMIC MEN

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SUMMARY
The hormonal effects of tamoxifen (10 mg daily for 6 months) have been studied in nine men with oligospermia. Basal concentrations of serum LH (1·7 ± 0·1 (s.e.m.) i.u./l) increased to a maximum of 4·1 ± 1·3 i.u./l (P < 0·001) after 6 months, and FSH rose from 4·9 ± 1·0 to a maximum of 7·7 ± 1·3 i.u./l after 4 months of treatment (P < 0·01).

The response to luteinizing hormone releasing hormone (LH-RH) was studied at monthly intervals. Sums of increments of serum LH increased from 35 ± 4 to 92 ± 17 i.u./l at 4 months (P < 0·001) and of FSH from 14 ± 3·4 to 23 ± 3·5 i.u./l at 4 months (P < 0·01).

Basal serum androgens rose from 25 ± 2·7 to 38 ± 2·4 nmol/l after 4 months of treatment (P < 0·05), and serum oestradiol-17β increased from 185 ± 25 to 631 ± 90 pmol/l by 6 months (P < 0·001). No significant changes occurred in sperm counts.

Five normal men acted as controls: they were given tamoxifen for 1 week. No significant changes were observed in serum LH, FSH or release of these hormones following administration of LH-RH. Serum androgens and oestrogens however, increased significantly by day 4 of treatment (P < 0·05).

INTRODUCTION
Tamoxifen is a non-steroidal derivative of triphenylethylene which has been shown to possess anti-oestrogenic properties in some mammalian species (Harper & Walpole, 1966); it is chemically related to clomiphene. Clomiphene citrate stimulates gonadotrophin release by competing with oestrogen at hypothalamic receptor sites (Kato, Kobayashi & Villee, 1968). Marshall, Anderson, Burke, Galvao-Teles & Fraser (1972) showed a rise in luteinizing hormone (LH), 17β-hydroxyandrogens, and cortisol in the blood following administration of the drug to normal men; increases in testosterone and cortisol were associated with increases in their respective binding globulins.

Idiopathic oligospermia is a common cause of male infertility, and the aetiology of the disorder is obscure. Attempts have been made to treat oligospermia with human menopausal gonadotrophin (Lytton & Mroueh, 1966), testosterone (Rowley & Heller, 1972), and clomiphene citrate (Heller, Rowley & Heller, 1969; Foss, Tindall & Birkett, 1973). Wieland, Ansari, Klein, Doshi, Hallberg & Chen (1972) treated 11 men with idiopathic oligospermia with a low dosage of clomiphene (5–10 mg daily) for 12 weeks. By week 12 of therapy there were significant increases in LH and testosterone, but rises in sperm counts occurred unpredictably. Despite inducing these hormonal changes clomiphene has generally proved to be an ineffective treatment for oligospermia.

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Clomiphene consists of a mixture of isomers and has been shown to exhibit both anti-oestrogenic and oestrogenic effects (Czygan & Schulz, 1972). The cis isomer has the properties of an anti-oestrogen, and Reyes & Faiman (1974) reported increased sperm counts, serum LH, testosterone and oestradiol concentrations after long-term therapy in infertile men. Tamoxifen is the trans isomer of 1-\((p\text{-dimethylaminoethoxyphenyl})\)-1,2-diphenyl-2-ethylethylen, which in some species behaves essentially as an anti-oestrogen (Harper & Walpole, 1967). It therefore seemed appropriate to evaluate this compound in the treatment of idiopathic oligospermia. A further aim of this investigation was to study the effect of the drug on pituitary and steroid hormones in patients with idiopathic oligospermia.

MATERIALS AND METHODS

The investigation was a single blind trial of tamoxifen (Nolvadex, I.C.I. Ltd) and placebo. Informed consent for the experimental treatment was obtained from all patients and controls. Nine patients were studied; all presented with infertility and sperm counts were persistently less than 30 \times 10^6/ml. They were all normal on physical examination and gave no history of orchitis, cryptorchidism or varicocele. All were judged not to have severe primary testicular disease since gonadotrophins were in the normal or lower normal range, and testicular size was normal. Each subject had a normal male karyotype.

The protocol comprised an initial month of placebo, followed by tamoxifen, 10 mg daily, for 6 months; this was then followed by a further 2 months of placebo. The subjects made monthly visits to the hospital bringing, on each occasion, a specimen of semen obtained that morning by masturbation after 4 days sexual abstinence. At each visit the subjects were given 100 \(\mu\)g luteinizing hormone releasing hormone (LH-RH) intravenously at 0 min via an indwelling cannula, and venous blood samples were obtained at -15, 0, 30 and 60 min. The serum was subsequently assayed for follicle-stimulating hormone (FSH), LH, total androgens and oestradiol-17\(\beta\) by radioimmunoassay (Shaw, Butt, London & Marshall, 1974; Duignan, Shaw, Rudd, Holder, Williams, Butt, Logan Edwards & London, 1975). Sex hormone binding globulin capacity (Rudd, Duignan & London, 1974) was determined on two patients before and during treatment.

A control group consisting of five normal men was also studied. After an initial LH-RH test these subjects took tamoxifen, 10 mg daily, for 1 week. LH-RH tests were repeated on days 4 and 7 of tamoxifen treatment and again 1 week after stopping treatment. It was not considered ethical to investigate the controls for a longer period.

The placebo tablets consisted of a starch base containing 1% chloroquine phosphate to provide a bitter taste. Tamoxifen was shown not to cross-react in the hormone assays.

RESULTS

The hormonal effects of tamoxifen are illustrated in Figs 1–3. The difference between the mean values for the treatment months and the control values were assessed by Student's \(t\)-test, analysis of variance and, where necessary, by the non-parametric method of Wilcoxon's Signed Rank test.

Infertile patients

Basal serum gonadotrophin levels

Before treatment three subjects had basal LH values below the normal range of 2–8 i.u./l. At the end of the initial month of placebo tablets the LH concentration was 1.7 ± 0.1 (s.e.m.) i.u. (d.f. = 8) and this increased significantly \((P < 0.001)\) to a maximum of 4.1 ± 1.3 i.u./l by week 24 of treatment with tamoxifen (Fig. 1a). The rise in basal LH was, however, already significant after only 1 month of therapy. With the reintroduction of placebo, LH
Values fell towards the control values and were no longer significantly increased after 2 months.

Tamoxifen produced a rise in mean basal FSH from $4.9 \pm 1.0$ to $7.7 \pm 1.3$ i.u./l ($P < 0.01$) by week 16 of treatment (Fig. 1b). The increase in FSH occurred more slowly than for LH and dropped to pre-treatment concentrations within 1 month of stopping treatment.

![Graph of Basal LH and FSH](image)

Fig. 1. Concentrations of (a) LH (i.u. MRC 68/40/1) and (b) FSH (i.u. MRC 69/104/1) in nine men undergoing tamoxifen therapy. Values are means ± S.E.M. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: significance of difference compared with basal concentrations.

Gonadotrophin response to LH-RH

The response is expressed as the sums of increments of serum LH at 30 and 60 min above the mean of the basal values. Treatment with tamoxifen produced increases in the sums of increments of LH from $35 \pm 4$ to $92 \pm 16.6$ i.u./l/60 min at 16 weeks ($P < 0.001$) (Fig. 2a).

Tamoxifen therapy produced an increase in the sums of increments of FSH after LH-RH from $14 \pm 3.4$ to a maximum of $23 \pm 3.5$ i.u./l/60 min at 16 weeks ($P < 0.01$) (Fig. 2b).
Steroid hormones

Before treatment basal serum androgen values were within the normal range of 10–40 nmol/l. Tamoxifen produced a rise in basal androgen values from 25 ± 2.7 nmol/l (Fig. 3a) at the beginning of treatment to 38 ± 2.4 nmol/l ($P < 0.05$) after 16 weeks.

Before treatment basal serum oestradiol values were within our normal range for adult males of 80–250 pmol/l. Tamoxifen produced a rise in basal oestradiol (Fig. 3b) from 185 ± 25 pmol/l to a maximum of 631 ± 90 pmol/l after 24 weeks ($P < 0.001$). The increase in oestradiol first became significant ($P < 0.05$) after treatment for 12 weeks.

Fig. 2. Response to LH releasing hormone, expressed as the sum of increments of serum (a) LH (i.u. 68/40/1) and (b) FSH (i.u. 69/104/1) in nine men undergoing tamoxifen therapy. Values are means ± S.E.M. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$: significance of difference compared with basal concentrations.
Fig. 3. Concentrations of serum (a) androgens (nmol/l) and (b) oestradiol (pmol/l) in nine men undergoing tamoxifen therapy. Values are means ± s.e.m. * P < 0.05; ** P < 0.01; *** P < 0.001; significance of difference compared with basal concentrations.
Sex hormone binding globulin capacity

The control values on the two patients examined were $4.3 \times 10^{-8}$ and $4.0 \times 10^{-8}\text{mol/l}$. During treatment with tamoxifen the values were $4.1 \times 10^{-8}$ and $4.3 \times 10^{-8}\text{mol/l}$ after 1 month and $4.6 \times 10^{-8}$ and $4.4 \times 10^{-8}\text{mol/l}$ after 2 months of therapy.

Sperm counts

No significant changes in sperm counts (Table 1) were observed in the group as a whole, but one subject who had an initial value of $2 \times 10^6/\text{ml}$ showed a transitory increase to $95 \times 10^6/\text{ml}$ and his wife became pregnant.

Other investigations

Blood counts and biochemical properties were monitored throughout the study and showed no significant changes.

Table 1. Sperm counts ($\times 10^6/\text{ml}$) before, during and after treatment with tamoxifen

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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<tr>
<td>0</td>
<td>5</td>
<td>28</td>
<td>0.5</td>
<td>7.0</td>
<td>0.2</td>
<td>2</td>
<td>—</td>
<td>0.2</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>53</td>
<td>1.5</td>
<td>0.9</td>
<td>0.3</td>
<td>24</td>
<td>1.4</td>
<td>1.0</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>35</td>
<td>1.6</td>
<td>0.7</td>
<td>0.3</td>
<td>25</td>
<td>1.8</td>
<td>0.4</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>—</td>
<td>1.7</td>
<td>0.5</td>
<td>0.7</td>
<td>20</td>
<td>5.0</td>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>36</td>
<td>1.4</td>
<td>0.7</td>
<td>0.1</td>
<td>34</td>
<td>0.3</td>
<td>1.6</td>
<td>6</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>28</td>
<td>4.0</td>
<td>0.4</td>
<td>0.3</td>
<td>95</td>
<td>1.3</td>
<td>0.1</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>70</td>
<td>50</td>
<td>6.0</td>
<td>0.5</td>
<td>0.6</td>
<td>20</td>
<td>3.0</td>
<td>0.1</td>
<td>14</td>
</tr>
<tr>
<td>24</td>
<td>45</td>
<td>18</td>
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<td>0.3</td>
<td>0.2</td>
<td>30</td>
<td>1.8</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>28</td>
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<td>2.0</td>
<td>0.7</td>
<td>0.4</td>
<td>30</td>
<td>2.0</td>
<td>0</td>
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<tr>
<td>32</td>
<td>33</td>
<td>—</td>
<td>0.9</td>
<td>0.3</td>
<td>0.5</td>
<td>20</td>
<td>4.0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>36</td>
<td>29</td>
<td>—</td>
<td>0.5</td>
<td>0.2</td>
<td>—</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>21</td>
</tr>
<tr>
<td>40</td>
<td>13</td>
<td>—</td>
<td>0.8</td>
<td>—</td>
<td>—</td>
<td>14</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

No treatment

Placebo

Tamoxifen

Placebo

Table 2. Mean hormonal levels in five normal male subjects and the effects of tamoxifen

<table>
<thead>
<tr>
<th>Day</th>
<th>Control</th>
<th>Tamoxifen (days 1-7)</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LH</td>
<td>FSH</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>1.4</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

LH-RH tests:

<table>
<thead>
<tr>
<th>Increments of</th>
<th>LH</th>
<th>FSH</th>
<th>Androgens</th>
<th>Oestradiol</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>17</td>
<td>5</td>
<td>24.6</td>
<td>273</td>
</tr>
<tr>
<td>FSH</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>503</td>
</tr>
<tr>
<td>Androgens</td>
<td>15</td>
<td>27.8</td>
<td>33.6</td>
<td>488†</td>
</tr>
<tr>
<td>Oestradiol</td>
<td>16</td>
<td>33.0†</td>
<td>488*</td>
<td>268</td>
</tr>
</tbody>
</table>

* The increase in androgens shows a significant linear trend ($P < 0.05$).
† Oestradiol was significantly raised during treatment ($P < 0.05$).
Normal volunteers

The summarized results on the five normal male volunteers are shown in Table 2. There were no significant changes in gonadotrophins, or in the amount of gonadotrophin released by LH-RH during treatment with tamoxifen. Serum androgens increased progressively and there was a significant linear relationship between the concentration and the length of treatment ($P < 0.05$). The level remained raised in the post-treatment specimen. Serum oestrogens also rose significantly immediately upon treatment ($P < 0.05$), and the level remained high until after treatment was discontinued when there was a significant decrease ($P < 0.05$).

DISCUSSION

The present data from the long-term studies of oligospermic men are consistent with an anti-oestrogenic action of tamoxifen. It is postulated that tamoxifen occupies oestrogen-binding sites in the hypothalamus and pituitary gland, and thus interferes with the normal negative feedback of sex steroids at this level; this results in increased gonadotrophin release.

The rise in androgens and oestradiol in the blood is interpreted as being secondary to the increased levels of gonadotrophins. Increased testicular production probably accounts for most of the increase in steroid hormones, but some peripheral conversion of androgen to oestrogens may also occur (MacDonald, Rombaut & Siiteri, 1967).

In the short-term control study, tamoxifen given for 7 days produced no change in basal serum LH or FSH, or in gonadotrophin response to LH-RH. However a significant rise in oestradiol and androgen in the circulation occurred, the mechanism of which is uncertain. It may be that tamoxifen produced transitory changes in gonadotrophin secretion too small to be detected in the two samples taken, but sufficient nevertheless to stimulate steroidogenesis. Alternatively, it might be speculated that tamoxifen stimulates the gonad directly, or alters its sensitivity to gonadotrophin, or that it has some effect on prolactin secretion.

The hormonal effects of tamoxifen in oligospermic men resemble those of clomiphene in that both compounds produce a rise in basal gonadotrophins and testosterone. In this investigation tamoxifen therapy enhanced the gonadotrophin response to LH-RH. There are no comparable data available on the long-term effects of clomiphene upon the LH-RH response in men. In a short-term study by Dhont, de Gezelle & Vandekerckhove (1976), the pituitary responsiveness to LH-RH was reduced in normal men given clomiphene. However Hashimoto, Miyai, Matsumoto, Izumi & Kumahara (1975) showed that basal gonadotrophins and testosterone in the circulation were raised in normal men treated with clomiphene, and in addition there was an enhancement of the FSH response to LH-RH. LH release was not however increased, possibly due to suppression by the increased testosterone concentration.

Despite the hormonal changes induced by tamoxifen, no significant change in sperm counts was observed. It therefore appears that tamoxifen is an ineffective treatment for idiopathic oligospermia when given in a dosage of 10 mg daily for 6 months. More prolonged therapy with higher dosages may however be more effective in increasing sperm count (Comhaire, 1976).

During the investigation one subject described two episodes of hot flushes; none of the others experienced these, and no other side-effects of tamoxifen were noted.

We are indebted to I.C.I. Pharmaceuticals for supplies of tamoxifen (Nolvadex), for statistical advice, and for a grant to carry out this investigation, and to Hoechst...
Pharmaceuticals and Ayerst Laboratories Ltd for supplies of LH-RH. We thank Dr J.
Crocker for the determinations of SHBG capacity.

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conversion of plasma Δ4-androstenedione to estrone in normal males and non pregnant normal, castrate
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