Biological Profile of Centchroman—A New Post-coital Contraceptive

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The biological properties of a new oral postcoital antifertility agent, Centchroman, 3, 4-trans-2, 2-dimethyl-3-phenyl-4-[-(3-pyrrolidinoethoxy)-phenyl-7-methoxy]chroman, have been investigated. A single oral administration of the compound within 24 hr of coitus prevented pregnancy in rats, mice (1.25 mg/kg), dogs and rhesus monkeys (2.5 mg/kg), and also intramuscularly in dogs (1.5 mg/kg); the minimum effective dose in rats in the days 1—5 post-coitum regime was 0.25 mg/kg. The antifertility effect was promptly reversible. It showed uterotrophic activity as rapidly as estrone both in immature rats and monkeys but induced vaginal cornification after a latent period in both the species the overall stimulation was about 50% of that of estrone. Centchroman was antiestrogenic and relatively more potent in inhibiting uterotrophic activity of estrone than in preventing estrone induced vaginal cornification. It was devoid of prostaglandin, androgenic and antiandrogenic properties but antagonized the action of progesterone in ‘Cueberg’, ‘Delayed Implantation’ and ‘decidua induction’ assays. The pituitary, thyroid and adrenal functions were not disturbed. The compound induced some foetal resorption (32%) in rats as compared to 14% in controls but no genital abnormalities or teratogenesis in neonatal sexual development and subsequent fertility was unimpaired. The transport, fertilization, development and viability of ovum was not disturbed in Centchroman treated rats since they implanted after receiving both estrogen and progesterone; there was, however, some arrest of ovum development and marked inhibition of decidua formation. Hence, Centchroman appeared to exert its antifertility action by virtue of its multiple hormonal attributes such as estrogenic, antiestrogenic and anti-progestational activities.

The chemical synthesis and structure-activity relationship of 3,4-diphenylchromones and chromans and the single dose antifertility activity of the most potent compound, 3-4-trans-2, 2-dimethyl-3-phenyl-4-[-(3-pyrrolidinoethoxy)-phenyl-7-methoxy]chroman (67/20 or Centchroman), of these series have been reported earlier from this Institute. This paper is concerned with the detailed biological evaluation of this new post-coital oral contraceptive, Centchroman. The data included in this communication have been submitted to the Drugs Controller (India) in the year 1970.

Materials and Methods

Albino rats (25-30, 50-60, 70-100 and 150-170 g), Swiss mice (6-8 and 25-35 g), rabbits (600-700 g and 2-3 kg) and rhesus monkeys (1.5-2 and 5-8 kg) of the Institute colony, and pure bred beagle dogs of the International Research and Development Corp., USA were used in this investigation. They were maintained in air-conditioned quarters (75°±2°F) under uniform husbandry conditions throughout the experimental period.

The compound (and estrone) was macerated with an equal quantity of gum acacia and suspended in distilled water for oral administration. The steroid hormones were dissolved in sterile olive oil for injection. The control animals received the vehicle alone in a similar manner.

Methods followed for the assessment of postcoital antifertility efficacy of Centchroman in rodents and rhesus monkeys, hormonal properties, mode of action, endocrine pharmacology and fetal effects were the same as employed previously.

For antifertility trials, pure bred adult mature female beagle dogs were mated with one of the two breeder male beagle dogs of proven fertility 11 and 13 days after a red vaginal discharge was first observed. The act of mating was directly controlled and observed, and the female was removed immediately after mating. Centchroman was administered intramuscularly or orally to female dogs 24 hr (day 2 of pregnancy) after mating. A batch of controls received sterile distilled water intramuscularly. Dogs were observed daily for characterization of vaginal discharge and for evidence of miscarriage or pharmacodynamic and toxic signs. After thirty-five days following the first mating, all the female dogs were sacrificed for examination of the ovaries, uterus, implantation sites and foetuses.

Results

Antifertility Efficacy

Rats and mice—Oral administration of Centchroman at doses of 0.25 mg/kg and above (up to 4 mg/kg) on days 1—5 post-coitum caused 100% prevention of pregnancy. At a slightly lower dose (0.2 mg/kg) the litter size was drastically reduced (versus control—p<0.01, 90%) whereas at a dose of 0.1 mg/kg (2/5th of 0.25 mg/kg) their number was still significantly less (versus Control—p<0.02, 57%) although 6 out of 8 rats were pregnant. Accordingly, 0.25 mg/kg is the minimum effective.
dose (ED<sub>100</sub>) in the days 1–5 regime in rats (Table 1). Likewise, in rats a single feeding of Centchroman at doses of 1.25 and 2.5 mg/kg on any one of the days 1–4 post-coitum was 100% effective in preventing pregnancy; on day 5 the litter size was considerably reduced (55–62%) at both the doses. A slightly lower dose (1 mg/kg) was fully effective (100%) in preventing pregnancy when administered on days 1.2 or 3, partially effective (60%), on day 4 and ineffective on day 5 post-coitum; 0.5 mg/kg dose was virtually ineffective. Thus 1.25 mg/kg is the minimum effective dose in the single day post-coitum regime (Table 2).

Mice — A single feeding of Centchroman (1.25 mg/kg) was 100% effective in preventing pregnancy in mice when given on days 1, 2 or 3 post-coitum; the litter size was also reduced on days 4 (60%) and 5 (40%) (Table 2).

Dogs — Centchroman administered once orally (2.5 and 5 mg/kg) or intramuscularly (1.5 and 2.5 mg/kg), 24 hr after mating, caused 100% prevention of pregnancy and there was no evidence of significant increase in uterine weight in immature dogs (Table 2).

Table 1 — Post-coital Antifertility Efficacy of Centchroman in Female Rats

<table>
<thead>
<tr>
<th>Dose mg/kg body wt</th>
<th>Days of pregnancy</th>
<th>No. of animals</th>
<th>No. of animals pregnant</th>
<th>No. of implantations (mean ± SE)</th>
<th>Litter size (mean ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (distilled water)</td>
<td>1–5</td>
<td>45</td>
<td>45</td>
<td>6.53 ± 0.33</td>
<td>5.73 ± 0.39</td>
</tr>
<tr>
<td>0.10</td>
<td>1–5</td>
<td>8</td>
<td>6</td>
<td>3.63 ± 1.05</td>
<td>3.25 ± 0.92</td>
</tr>
<tr>
<td>0.20</td>
<td>1–5</td>
<td>11</td>
<td>3</td>
<td>0.73 ± 0.40</td>
<td>0.73 ± 0.40</td>
</tr>
<tr>
<td>0.25</td>
<td>1–5</td>
<td>50</td>
<td>0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td>0.5, 1, 2, 4</td>
<td>1–5</td>
<td>6, 6, 6, 6</td>
<td>0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
</tbody>
</table>

Table 2 — Effect of a Single Oral Dose of Centchroman in Rats, Mice, Dogs and Monkeys

<table>
<thead>
<tr>
<th>Dose mg/kg body wt</th>
<th>Days of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Rats</td>
<td></td>
</tr>
<tr>
<td>Controls (distilled water)</td>
<td>5.73±0.39 (45)</td>
</tr>
<tr>
<td>0.5</td>
<td>3.50±1.16 (8)</td>
</tr>
<tr>
<td>1.0</td>
<td>0.0 ± 0.0 (17)</td>
</tr>
<tr>
<td>1.25</td>
<td>0.0 ± 0.0 (48)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.0 ± 0.0 (6)</td>
</tr>
<tr>
<td>Mice</td>
<td></td>
</tr>
<tr>
<td>Controls (distilled water)</td>
<td>6.56±0.54 (16)</td>
</tr>
<tr>
<td>1.25</td>
<td>0.0 ± 0.0 (12)</td>
</tr>
<tr>
<td>Dogs</td>
<td></td>
</tr>
<tr>
<td>Controls (distilled water)</td>
<td>7.00±2.34 (4)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.00±0.00 (4)</td>
</tr>
<tr>
<td>5.0</td>
<td>0.00±0.00 (4)</td>
</tr>
<tr>
<td>5.0 (im)</td>
<td>0.00±0.00 (4)</td>
</tr>
<tr>
<td>Rhesus monkeys</td>
<td></td>
</tr>
<tr>
<td>Controls (distilled water)</td>
<td>1±0 (6)</td>
</tr>
</tbody>
</table>

Rhesus monkeys — Oral administration of Centchroman (2.5 mg/kg) on the day following the coital act (only once per cycle/4–5 cycles) caused cent per cent prevention of pregnancy during a 6 month trial. The post-coital antifertility efficacy score was, therefore, 0 over 80 monkey months. In controls, 4 out of 6 animals became pregnant in 20 monkey months and delivered healthy babies; the remaining 2 controls did not become pregnant in 14 monkey months involving 11 positive matings over 11 cycles (Table 2).

Reversibility of antifertility effect — Centchroman (0.25 mg/kg, days 1–5; 1.25 mg/kg, days 1, 2 or 3) administration did not lead to permanent sterility in rats, since discontinuation of the treatment caused prompt return to normal fertility.

Hormonal Properties

Estrogenic activity — Oral (0.1, 0.25, 0.5, 1.25 and 2.0 mg/kg) or subcutaneous (1, 5, 10, 50 and 100 µg/animal) administration of Centchroman caused a significant increase in uterine weight in immature rats (versus controls, P<0.01, Table 3). The uterotrophic potency was 40–50% of that of estrone by the oral route and about 23–44% parenterally.
The uterine epithelium consisted of tall spindle shaped cells with a basal arrangement of nuclei. The stroma was slightly loose and fibroblast-like cells predominant. The epithelium of estrone treated rats was, however, apparently more stimulated as indicated by the presence of mitotic figures. The stroma was loose and edematous; the fibroblast-like elements were predominant. Like­wise, in immature rhesus monkeys, oral administration of Centchroman (1.25 mg/kg) daily for 5 days caused an increase in uterine weight and induced vaginal cornification (Table 3). The uterotrophic potency was about 64% of that of estrone. The number of cornified cells in vaginal smears was considerably higher (++) than that of controls (0 to +) but notably less than that of estrone treated animals (+++). There was reddening of the sex skin. The breasts were only slightly enlarged, and the nipples were prominent. Estrone treatment, on the other hand, caused marked swelling and edema of the circumgenital area, reddening of the sex skin and the nipples were more prominent and erect. However, withdrawal bleeding was not seen in either Centchroman or estrone treated animals.

Duration of estrogenic activity — A single feeding of estrone or Centchroman (1.25 mg/kg) was equipotent in stimulating uterine weight in immature female rats (Fig. 1). The uterotrophic activity reached its peak 2 days after administration of the compound or estrogen (versus 0 day control—P < 0.01; versus 2 day control—P < 0.01), significantly declined thereafter (2 days versus 5, 7 or 10 days—P < 0.01) and became virtually nil by 15 days. Thus the duration of uterotrophic activity was similar after Centchroman and estrone treatments.

Estrone induced vaginal cornification, ('estrus' type smears) and this condition persisted between 2 and 7 days post-treatment. Proestrus/estrus type smears were produced by Centchroman but not until 5 days and lasted till day 7.

Antiestrogenic activity — Injection or oral administration of estrone (1 µg/animal) to immature female rats stimulated uterine weight and caused vaginal cornification ('estrus' type vaginal smear) at all
doses (versus control—P<0.01; Table 4). Simultaneous administration of estrone (1 μg/animal) and Centchroman (0.125 to 5 mg/kg), oral or parenteral, also caused a significant increase in uterine weight (versus control—P<0.01) but the extent of uterotrophic response was less than that produced by estrone alone (P<0.01; Table 4). The vaginal cornification was also suppressed (proestrus/estrus type) at all the doses after subcutaneous administration and at high doses (2.5 and 5 mg/kg) only in those rats that received Centchroman by oral route. The histological features of the uterus were similar to those of compound alone group. Thus Centchroman showed antierutrophic activity.

In 'delayed implantation' test, there was no effect on number of implantations after concurrent administration of progesterone (6 mg, sc), estradiol dipropionate (1 μg, sc) and Centchroman (0.25 mg/kg, oral) from days 8–12 of pregnancy (versus controls—P>0.5; Table 5). Thus, Centchroman did not show any antiestrogenic activity in this test. Centchroman per se did not induce implantation in this assay.

**Progestational and antiprogestational activity** — In Clauberg assay, oral administration of Centchroman (0.25 mg/kg/day for 5 days) alone did not produce any proliferative changes in the endometrium of immature rabbits and the histological picture was typically infan tile. Whereas progesterone (0.75 mg/day for 5 days, oral) caused stage II or III (+ + + ) type proliferative changes (in McPhail scale) in the endometrium. The administration of the compound along with progesterone prevented the proliferative changes seen when the latter alone was given; the histological picture was similar to Centchroman per se group.

In 'delayed implantation' test, the administration of Centchroman (0.25 mg/kg, oral) in combination with progesterone (days 3–8 of pregnancy) completely prevented implantation (versus control — P<0.01; Table 5).

Thus Centchroman showed antiprogestational activity both in Clauberg assay and 'delayed implantation' test.

**Androgenic and antiandrogenic activity** — Testosterone propionate (10 mg/kg for 7 days, im) stimulated seminal vesicle and ventral prostate weight in castrated rats (P<0.01; Table 6); Centchroman on the other hand, had no effect. Combined treatment with testosterone propionate and the compound did not antagonize the effect of the former on the weight of the accessory genital organs (P>0.9).

**Endocrine Pharmacology**

**Effect on pituitary** — Centchroman (1.25 mg/kg for 7 days, oral) had no effect on weight and total gonadotrophin content of the young male rat pituitary (versus controls—P>0.9; Table 7). The weight and histology of the genital organs also remained unchanged.

**Effect on thyroid** — Centchroman (1.25 mg/kg for 5 days, oral) had no significant effect on thyroid weight, 131 I uptake and 'conversion ratio' in immature female rhesus monkeys (Table 8).

**Effect on adrenal** — Centchroman (1.25 mg/kg for 5 days, oral) did not influence the excretion rate
Thus a high percentage of blastocysts (normal or degenerating) reached 60% on day 6 of pregnancy. The ova collected from the Fallopian tube on day 1 of pregnancy to rats did not impede transport and fertilization of ova. There was arrest of development in about 30% of the ova.

Effect of ova — Centchroman (1.25 mg/kg) administered orally on day 1 of pregnancy to rats did not impede transport and fertilization of ova. There was, however, arrest of development in about 30% of the ova. The ova collected from the Fallopian tube on day 1 were freshly fertilized 1- and 2-celled, on days 2 to 3 were 2- and 4-celled; none were recovered from the uterus (Table 10). The development of about 30% of the fertilized ova was arrested on days 2 and 3 of pregnancy. On day 4, all the ova were normally developing morulae and were recovered both from the Fallopian tube and the uterus. About 15% of the blastocysts appeared moribund on day 5 and this number reached 60% on day 6 of pregnancy. Thus a high percentage of blastocysts (normal or degenerating) could be collected from the uterus of 24 hr urinary 17-OH-KGS in immature female rhesus monkeys whereas estrone caused a slight increase (versus control — P<0.02) (Table 8).

Effect on foetus and fertility of the offspring

Effect on foetus — Oral administration of Centchroman (1.25 and 2 mg/kg) on days 5-7 of pregnancy to rats had no effect on the developing blastocyst or the newly implanted foetus (Table 9); however, 17-32% less blastocysts implanted as compared to controls. A single feeding (1.25 mg/kg on day 8 of pregnancy, however, caused 30% fetal loss in compound treated rats as against 14% in controls (Table 9). There was no deleterious effect on the genital organs of the foetus or the neonates as revealed by histologic examination. No fetal masculinization or teratogenicity was, however, noticed.

Effect on progeny — The fertility performance of the offspring was studied for 2 generations, and no detrimental effect was recorded.

Mechanism of action

Effect on ova — Centchroman (1.25 mg/kg) administered orally on day 1 of pregnancy to rats did not impede transport and fertilization of ova. There was, however, arrest of development in about 30% of the ova.

Histologically, the traumatized uterine horn of control rats showed endometrium lined with cuboid epithelium. The stroma was slightly edematous and consisted mostly of decidual cells with occasional polymorphonuclear leucocytes. In contrast, the traumatized horn of compound treated animals showed massive decidual swellings. Histologically, the traumatized uterine horn of control rats showed endometrium lined with cuboid epithelium. The stroma was slightly edematous and consisted mostly of decidual cells with occasional polymorphonuclear leucocytes. In contrast, the traumatized horn of compound treated animals showed massive decidual swellings. Histologically, the traumatized uterine horn of control rats showed endometrium lined with cuboid epithelium. The stroma was slightly edematous and consisted mostly of decidual cells with occasional polymorphonuclear leucocytes. In contrast, the traumatized horn of compound treated animals showed massive decidual swellings.

Effect of estrogen and progesterone on antifertility action — A single feeding of Centchroman (1.25 mg/kg) on day 1 of pregnancy prevented decidua formation in tubectomized, ovariectomized and traumatized rats treated with progesterone (2 mg daily) for 3 days. In controls, the traumatized horn was significantly heavier than its contralateral horn and that of Centchroman treated animals (P<0.01) and showed massive decidual swellings.
mg/kg on day 1 of pregnancy) caused 100% prevention of implantation in rats. Progesterone (5 mg/rat) given to compound treated animals from days 1-5 or 1-10 of pregnancy failed to induce implantation. However, the same hormone (days 1-10) administered in combination with estradiol dipropionate (1 μg/rat, days 5-10) induced high percentage of implantations. If estrogen therapy was delayed and given from days 10-15 along with progesterone (days 1-15), the number of implantations was significantly less (versus control—P<0.01) and only 50% of that seen in the normal controls or in the former conjoint group. Estradiol dipropionate per se did not induce implantation in compound treated animals (Table 11). Thus Centchroman interfered with the action of both the estrogen and progesterone since neither of these hormones per se could induce implantation in compound treated rats.

Discussion

The results of the present study show that Centchroman is a potent post-coital antifertility agent. A single oral administration of the compound within 24 hr of the coital act causes 100% prevention of pregnancy in rats, mice (1.25 mg/kg), dogs and rhesus monkeys (2.5 mg/kg); it is equally effective intramuscularly in dogs (1.5 mg/kg) and intravaginally in rats. In rats and mice, a single oral administration on any one of the days 1 to 3 of pregnancy prevents implantation. The minimum effective dose in the days 1 to 5 post-coitum regime is 0.25 mg/kg. Fertility of animals returns promptly following withdrawal of the treatment. The antiimplantation properties of nonsteroidal antifertility agents possessing weak estrogenicity and antiestrogenicity have been extensively reviewed. These reviews show that only potent estrogens (e.g. diethylstilbestrol, ORF-3858) or a weak estrogen with potent antiestrogenic and some antiprogestational activities (e.g. NF) are effective in preventing conception in monkeys; none of the non-steroidal weak estrogens with potent antiestrogenicity are effective in monkeys. On the other hand, a progestogen with potent anti-estrogenic property (Norgestrel) has shown post-coital antifertility activity in human.

Centchroman shows uterotrophic activity and induces vaginal cornification both in immature rats and rhesus monkeys. Although its effect on the uterus is as rapid as that of estrone, it has a latent period in causing vaginal cornification. However, the duration of uterotrophic activity is more or less similar. Nonetheless, in all the indices, it appears to be a weak estrogen since the stimulation was only about 50% of that of estrone. This is further supported by its failure to induce nida in rat in a delayed implantation test. Furthermore, it has been reported that Centchroman does not stimulate all the classical biochemical responses in uterus and

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**Table 10 — Effect of a Single Oral Dose of Centchroman on Rat Ova**

<table>
<thead>
<tr>
<th>Dose (1.25 mg/kg body wt on day 1 of pregnancy)</th>
<th>Day of collection of ova of animals (No.)</th>
<th>Total no. of corpora lutea (No.)</th>
<th>Total no. of ova collected</th>
<th>Fallopian tube</th>
<th>Uterus</th>
<th>No. and stage of development</th>
<th>No. with arrested development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (distilled water)</td>
<td>2 (4)</td>
<td>33</td>
<td>24</td>
<td>0</td>
<td>22</td>
<td>(2-cell)</td>
<td>2 (1-cell fertilized)</td>
</tr>
<tr>
<td></td>
<td>3 (2)</td>
<td>13</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>(2, 4-cell)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4 (2)</td>
<td>18</td>
<td>7</td>
<td>0</td>
<td>(Morula)</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5 (2)</td>
<td>16</td>
<td>8</td>
<td>(Blastocyst)</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (3)</td>
<td>24</td>
<td>0</td>
<td>3</td>
<td>(Blastocyst)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td>Centchroman</td>
<td>1 (10)</td>
<td>77</td>
<td>36</td>
<td>0</td>
<td>(1-cell fertilized or 2-cell)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (7)</td>
<td>64</td>
<td>33</td>
<td>0</td>
<td>(2-cell)</td>
<td>13</td>
<td>4 (1-cell, fertilized)</td>
</tr>
<tr>
<td></td>
<td>3 (6)</td>
<td>45</td>
<td>17</td>
<td>0</td>
<td>(2, 4-cell)</td>
<td>36</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4 (8)</td>
<td>74</td>
<td>7</td>
<td>29</td>
<td>(Morula)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (5)</td>
<td>43</td>
<td>0</td>
<td>15</td>
<td>(Blastocyst)</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>6 (5)</td>
<td>44</td>
<td>0</td>
<td>18</td>
<td>(Blastocyst, degenerating)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Table 11 — Effect of Estrogen and Progesterone on Antifertility Effect of Centchroman**

[Dose of Centchroman is 1.25 mg/kg body wt, progesterone 6 mg/rat and estradiol dipropionate 1 μg/rat]

<table>
<thead>
<tr>
<th>Treatment (days post-coitum)</th>
<th>No. of animals</th>
<th>No. of implantations (mean ±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>45</td>
<td>6.53 ±0.33</td>
</tr>
<tr>
<td>Centchroman (1)</td>
<td>48</td>
<td>0.00 ±0.00</td>
</tr>
<tr>
<td>Centchroman + Progesterone</td>
<td>14</td>
<td>0.00 ±0.00</td>
</tr>
<tr>
<td>Centchroman + Progesterone</td>
<td>14</td>
<td>0.00 ±0.00</td>
</tr>
<tr>
<td>Centchroman + Progesterone</td>
<td>15</td>
<td>5.80 ±1.04</td>
</tr>
<tr>
<td>Estradiol dipropionate (5-10)</td>
<td>8</td>
<td>3.25 ±1.17</td>
</tr>
<tr>
<td>Centchroman + Progesterone</td>
<td>15</td>
<td>5.80 ±1.04</td>
</tr>
<tr>
<td>Estradiol dipropionate (10-15)</td>
<td>16</td>
<td>0.00 ±0.00</td>
</tr>
</tbody>
</table>

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uterine fluid of rat like estrogen\textsuperscript{14} thereby revealing its weak or atypical estrogenicity. The pituitary, adrenal and thyroid functions are not disturbed.

Centchroman is antiestrogenic and is relatively more potent in inhibiting uterotrophic activity of estrone than in preventing estrone induced vaginal cornification. This finding has been corroborated recently\textsuperscript{18}.

Centchroman is devoid of progestational activity but it antagonizes the action of progesterone in Clauberg, 'delayed implantation' and deciduoma induction assays. In contrast, it has been reported that Centchroman does not interfere with the uptake of labelled progesterone by the target tissues\textsuperscript{18}. This is rather enigmatic and demands further studies. The compound is devoid of androgenic and anti-androgenic properties.

Centchroman causes some foetal resorption in rats when administered peri or post-implantation. Such effects have been reported to be associated with several other estrogenic compounds\textsuperscript{14}. Nevertheless, no abnormal genital development or teratogenicity has been found in the foetus, and their post-natal sexual development and subsequent fertility potential remain unimpaired.

The antifertility action of Centchroman seems to be at the level of both the Fallopian tube and the uterus since there is some arrest of egg development and marked inhibition of deciduoma formation. The transport, fertilization, development and viability of majority of the ova is not disturbed since implantation occurs in Centchroman treated rats superimposed with both progesterone and estrogen. Neither of these steroids per se induce implantation. Thus, Centchroman appears to exert its antifertility effect by interfering with the action of both estrogen and progesterone. This has been adequately revealed by a number of bioassays employed in this study, i.e. 'delayed implantation', deciduoma induction, Clauberg assay, substitution with estrogen and progesterone. Thus, it is likely that Centchroman prevents implantation by its multiple attributes such as estrogenic, antiestrogenic and antiprogestational activities. To this may be added the property of its causing arrest of ova development, and all of these collectively make this compound a fairly potent post-coital contraceptive.

Acknowledgement

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References