Effect of Megestrol Caproate on the Reproductive Function of Laboratory Animals

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In vivo experiments on rats and rabbits showed that megestrol caproate, a 17-α-hydroxyprogesterone derivative exhibits 10-fold higher gestagenic activity compared to progesterone and possesses no androgenic, anabolic, and estrogenic activities.

Key Words: *progestagens; estrogens; steroids; oral contraceptives*

It was previously shown that pregnane steroids, including megestrol caproate, are characterized by low nonspecific toxicity [3,4]. In contrast to norsteroid compounds pregnane derivatives produce no androgenic, anabolic, and estrogenic effects [4,9,12], which, along with their gestagenic activity allows their wide use for hormone therapy in obstetrics and gynecology and for contraception. We studied gestagenic, androgenic, anabolic, and estrogenic activities of megestrol caproate (17α-caproate-6-methylpregna-4,6-diene,3β, 17α-diol-20-on) synthesized at Center of Drug Chemistry, Chemical Pharmaceutical Institute (Moscow) [10,14].

MATERIALS AND METHODS

Experiments were carried out on young Wistar rats (89 males and 24 females, 40-60 g) and 56 infantile female Chinchilla rabbits (700-1000 g) from Rappolovo Breeding Center of Russian Academy of Medical Sciences. All animals were kept under standard vivarium conditions at D. O. Ott Institute of Obstetrics and Gynecology and fed standard diets.

Gestagenic activity of the test compound was studied on rabbits using a modified method [6,13]. Experimental animals were daily subcutaneously injected with megestrol caproate in increasing doses (0.004, 0.016, 0.0625, and 0.25 mg/kg) for 5 days. Controls received progesterone according to the same protocol. Progestagenic activity was evaluated by the degree of secretory transformation of the endometrium (Klauberg test) [2,6,7,13]. The results were statistically processed by regression analysis. The regression equation was as follows:

$$y=a+b\log(x),$$

where y is McPhail index, x gestagen dose, a and b regression coefficients. Biological activity was eva-

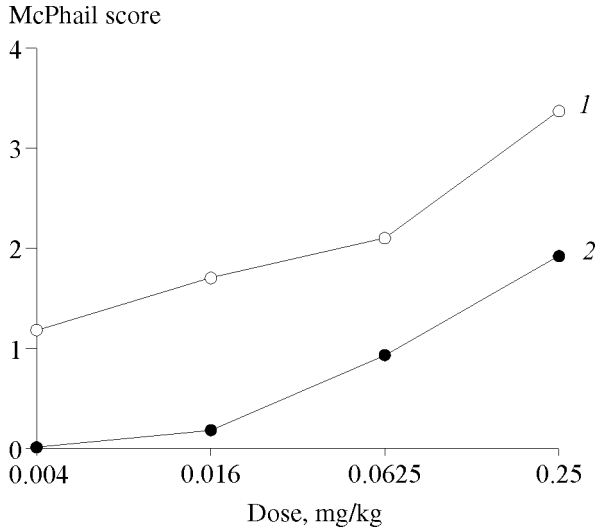

Fig. 1. Secretory transformation of rabbit endometrium after subcutaneous treatment with megestrol caproate (*1*) and progesterone (*2*) in the Klauberg—McPhail test.

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luated by the effective dose producing a pharmacological effect in 50% cases (ED_{50}, corresponded to 2 points according to McPhail scale) and expressed in mg/kg. The relative progestagenic activity (RA) was estimated taking progesterone activity for 1 [1,6,12].

Androgenic and anabolic activity was studied on castrated male rats by the method of Hershberger [2, 6,8]. The animals were divided into 3 groups (15-20 rats per group). Group 1 animals were injected with the test drug, group 2 rats were injected with testosterone propionate in a dose of 2.5 mg/animal, and group 3 animals (controls) received the same volume of the solvent (vegetable oil). The preparations were injected intramuscularly for 7 days starting from the day of castration. On day 8 the animals were sacrificed. Androgenic activity was evaluated by the weight of the ventral prostate and seminal vesicles, anabolic activity was evaluated by the weight of *m. levator ani.*

Uterotropic (estrogenic) activity was studied on young female rats by the method of Dorfman [1,11]. Experimental rats were intramuscularly injected with megestrol caproate (oil solution) for 3 days; controls received the solvent. After that the animals were sacrificed, autopsied, and the uteri were weighed.

The test drug was injected in a dose of 1.5 mg/kg, which 6-fold surpassed the effective dose.

RESULTS

Subcutaneous injection of megestrol caproate in a dose of 0.25 mg/kg produced a pronounced gestagenic effect and induced secretory transformation of the endometrium (3.3 points according to the McPhail scale). The gestagenic effect gradually decreased with decreasing the dose (Fig. 1).

The gestagenic activity of megestrol caproate was 10.2 times higher than that of progesterone injected subcutaneously (Table 1). No significant changes in the weight of seminal vesicles, ventral prostate (at $p<0.01$), and *m. levator ani* (at $p<0.05$) were detected in experimental animals treated with megestrol caproate, which indicated the absence of androgenic and anabolic effect of this drug (Table 2).

The weight of the uterus was 53.73±9.69 and 52.59±4.79 mg in experimental and control animals, respectively ($p<0.05$). Hence, megestrol caproate in the studied dose induced no appreciable changes in the weight of the uterus of infantile rats (*i.e.* produced no uterotropic effect).

TABLE 1. Gestagenic Activity of Megestrol Caproate (0.004-0.250 mg/kg) and Progesterone (0.125-1.0 mg/kg) in Subcutaneous Treatment (Klauberg—McPhail Test)

Parameter	Progesterone (n=30)	Megestrol caproate (n=21)
Parameters of dose—effect curve		
a	2.85	3.83
b	1.47	1.17
ED_{50}, mg/kg	0.27	0.0266
RA	1	10.15

Hence, megestrol caproate possesses high gestagenic activity (10.2 times higher than that of progesterone at parenteral administration) and produces no androgenic, anabolic, and estrogenic effects. This suggests that megestrol caproate can be used as a gestagenic agent. These data are of theoretical and practical importance and prompt further studies of megestrol caproate, which can be used for the creation of contraceptives and therapeutic agents.

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TABLE 2. Effect of Megestrol Caproate on the Weight of Target Organs in Castrated Infantile Male Rats ($M\pm m$)

Weight, mg	Control (0.1 ml solvent)	Testosterone, 2.5 mg/rat	Megestrol caproate, 1.5 mg/kg
Ventral prostate	11.64±1.89	36.88±1.49*	11.53±1.18
Seminal vesicles	14.62±1.29	107.45±3.75*	13.53±3.39
M. levator ani	55.99±8.75	212.43±9.98*	54.33±8.13

Note. *$p<0.05$ compared to the control.

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