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Effect of Aminoglutethimide on Serum Progesterone and Estrogen in the Pregnant Baboon (Papio SP) (38632)

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Aminoglutethimide (AG) inhibits the conversion of cholesterol to pregnenolone and thereby interrupts steroid synthesis in organs such as the adrenal, ovary, testis, and placenta (1–5). The ability of AG to block the production of estrogens and progesterone by the ovary and placenta has suggested its use as a possible antifertility drug. Glasser *et al.* (2) induced abortion on the ninth day of pregnancy in rats by repeated injections of AG. Termination of pregnancy was correlated with very low serum progesterone levels and could be prevented by exogenously administered progesterone (2). Salhanick *et al.* have shown that AG binds to human ovarian and placental cytochrome P450 *in vitro* and in large doses reduces urinary pregnanediol levels in pregnant women (4, 5). The reduction in pregnanediol (approximately 50%) was not followed by abortion. We were interested in investigating the effects of repeated and even larger doses of AG on pregnancy in a subhuman primate. The menstrual cycle and early pregnancy in the baboon are in many respects similar to those of human beings, and we therefore selected this animal for our study. AG dramatically reduced serum progesterone levels in five of six baboons but did not induce immediate abortion.

Materials and Methods. Six adult female baboons were selected for the study from the LEMSIP colony on the basis of regular menstrual cycles, normal reproductive tract, and general good health. Near the end of the period of maximum turgescence of the sex skin (generally cycle days 14–16) the animals were placed in breeding cages with adult males. Intromission was confirmed by observation of a semen plug or detection of spermatozoa in the vaginal smear. Pregnancy was determined on about the 30th day of gestation by palpation of the uterus, observed discontinuance of phasic sex skin changes and elevated serum estrogen and progesterone levels. Racemic[1] AG (1 g dose) as the phosphate salt or *d*-AG (0.5 g dose) as the tartrate salt were prepared in gelatin capsules. The compounds were administered orally twice daily at 9 AM and 3:00 PM for 1 or 3 days. Blood samples were drawn for steroid determinations before and at various time intervals after giving the initial capsule.

Serum progesterone levels were measured by the radioimmunoassay of Abraham *et al.* (6) as previously modified in our laboratory (7). Serum total estrogens were determined by radioimmunoassay according to Abraham *et al.* (8) as modified by Giannina and Leathem (9). Both antisera (S49 No. 6 for progesterone; S52 No. 5 for estradiol) were supplied by Dr. Abraham.

The animals were observed until pregnancy was terminated either by abortion or by delivery at term.

Results. Oral administration of AG (1 g racemic AG or 0.5 g d-AG twice daily) was followed in 6 hr by a precipitous drop in serum progesterone concentration (Table I, baboons number B-188, B-198, and B-418). At 24 hr the progesterone level had returned essentially to normal in B-418, but was even further depressed (only 6% of initial) in B-188. The 24 hr serum sample for B-198 was lost. Serum estrogens were likewise depressed 6 and 24 hr after AG administration in B-188 (Table I). The treatment period with racemic AG was expanded to 1 gm twice daily for 3 consecutive days in three baboons (Table I). In B-186 (50 days pregnant), serum progesterone fell 29% in 24 hr and 81% by 72 hr. In B-486, serum progesterone dropped to 35% of pretreatment level in 6 hr, to 18% in 24 hr, to 3.2% in 48 hr, and was still less than 10% at 72 hr

[1] Elipten, CIBA-GEIGY.

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TABLE I. EFFECTS OF AMINOGLUTETHIMIDE ON PLASMA PROGESTERONE AND ESTROGEN LEVELS IN PREGNANT BABOONS.

Baboon No.	Days pregnant	Treatment	Serum progesterone ng/ml					Serum extrogens pg/ml	
			Pre-treatment	6 hr	24 hr	48 hr	72 hr	Pre-treatment	Post-treatment[a]
B-188	73	AG 1 g b.i.d. × 1	37.9	7.6	2.1	—		470	202
B-198	73	AG 1 g b.i.d. × 1	24.8	5.1	lost	—	—	—	—
B-418	99	d-AG 0.5 g b.i.d. × 1	33.9	5.6	30.9	—	—	—	—
B-186	50	AG 1 g b.i.d. × 3	25.7	—	18.3	—	5.1	150	75
B-486	67	AG 1 g b.i.d. × 3	26.2	8.8	4.7	0.8	2.4	508	240
B-596	31	AG 1 g b.i.d. × 3	9.4	—	15.8	15.5	—	110	100

[a] Taken at time of last progesterone sample.

(Table I). Her serum estrogen level was depressed by more than 50% (Table I). In B-596 serum progesterone was initially low and if anything increased at 24 hr and 48 hr after treatment (Table I). Serum estrogens were essentially unchanged by AG in this baboon. None of the baboons aborted during or for at least 3 wk after the experiment. B-486 and B-596 subsequently aborted at 139 and 54 days of gestation respectively (69 and 20 days after AG treatment). It should be remembered that B-596 showed no drop in serum progesterone during treatment with AG. Furthermore, a control animal unconnected with the AG study also aborted early in pregnancy. Thus, none of the abortions could definitely be ascribed to, and were probably not a result of the drug treatment.

Discussion. Administration of AG was associated with severely depressed serum progesterone and estrogen levels in five or six pregnant baboons. The primary source of sex steroids at the stages of pregnancy examined in baboons (31–99 days) is not definitely known. However, in other primates (e.g., rhesus monkey) the placenta becomes the major source of estrogen and progesterone after the 21st day of pregnancy, while ovarian steroid secretion wanes (see 10). If a similar shift of steroid production from ovary to placenta prevails in the baboon, it may be assumed that the effect of AG is exerted primarily on steroid producing enzymes in the placenta. Salhanick *et al.* (4, 5) have shown that AG binds to human placental cytochrome P450, and it is thus likely that AG also interferes with the cytochrome system in the baboon. Unlike the rat, which aborts in a short time after its serum progesterone levels are reduced by AG administration (2), the baboon seems to be capable of maintaining pregnancy after a prolonged (72 hr) severe depression of peripheral progesterone concentration. Salhanick *et al.* (4, 5) observed about a 50% decrease in urinary pregnanediol levels but no abortions in pregnant women treated with AG. Presumably this 50% reduction in pregnanediol excretion reflects a like decrease in progesterone secretion (although it is also conceivable that AG could alter the metabolic fate of progesterone). In our studies progesterone secretion was decreased even further (80–96%) by AG and yet immediate abortion did not occur. It remains to be established whether or not pregnancy in the baboon could survive an even longer period of suppressed progesterone and estrogen secretion. However, the data strongly suggest that in this species, peripheral serum sex steroid levels may not reflect the concentration of these hormones at their most important target, the uteroplacental juncture.

Summary. AG was administered orally twice daily for 1 or 3 days to six baboons whose duration of pregnancy ranged from 31 to 99 days. Serum progesterone levels were reduced to as little as 3.2% of the initial concentration in one animal and to 20% or less in four of the five remaining baboons. Serum estrogen levels were depressed by 50% or more in three of the four animals in which they were measured. However, pregnancy ensued for at least 3 wk after treatment in all animals. The data suggest that peripheral

blood levels of sex steroids may not reflect the critical concentration of hormones required at the uteroplacental juncture for successful pregnancy maintenance.

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