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SELECTION OF STEROIDS FOR INCORPORATION INTO SILASTIC INTRAUTERINE DEVICES

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SUMMARY

Progesterone, five synthetic progestins and one non-steroidal uterine relaxant were incorporated into silastic IUD's at levels at 5 and 10% total weight of the device in an effort to increase efficacy and decrease the rate of expulsion of the devices. Initial studies in rodents indicated that all compounds had some effect, the synthetic progestins being best. Five per cent devices did not inhibit mating while 10% did. The rate of release of four synthetic steroids was determined in rats, and that of medroxyprogesterone acetate in patas and rhesus monkeys as well. This latter steroid has been incorporated into IUD's (75–150 mg total dose) which have been used in women with very promising results. Two additional synthetic progestins, norgestrel and norethindrone, as well as Provera are being used in baboon IUD's with only Provera enhancing retention. The effect of daily microgram release rates of Provera on the menstrual cycle and perineal swelling is variable and reversible with removal of the device.

INTRODUCTION

The small number of pregnancies that occur with an IUD *in situ* may deter some women from choosing this method of family planning; but a far larger segment of the population will not use or will discontinue use of the IUD because of expulsion or the bleeding and spotting associated with all IUD's currently on the market. Modifications in size, shape or material of the devices have not completely solved these problems; however, using the device to deliver microquantities of bioactive substances that act locally on the uterus may abolish these undesirable side effects while combining the effectiveness of steroid contraception with the ease of use of IUD's.

Preliminary studies in rodents and subhuman primates had shown that when melengestrol acetate, MGA, an extremely potent synthetic progestin, was incorporated into silastic IUD's, 80–100% of rats retained the devices while less than 20% of controls had their devices *in situ* at the end of the same 2 week period [1, 2]. Animals with devices containing 5% by weight of the hormone in one horn continued to cycle, mated and had normal implantations in the control horn. Devices with 10% MGA exhibited 100% retention; however, less than 20% of these animals mated and none had implantations. *In vivo* uterine motility studies done on rats with a control device in one horn and a 5% MGA releasing device in the contralateral horn demonstrated a decrease in frequency and amplitude of contractions in the horn with the progestin releasing IUD.

Our conclusions from these preliminary trials were that the 5% MGA device caused an increase in IUD retention by a local effect on the uterus and did not interfere with other reproductive processes, but 10% MGA devices apparently had a systemic effect that inhibited reproduction.

Encouraged by these positive findings, we set up a study in rodents to screen possible compounds and select promising ones for further testing in primates and eventually humans. Results of these studies to date are the subject of this report.

EXPERIMENTAL RESULTS

Copper, isoxsuprine, (a non-steroidal uterine relaxant), progesterone and five synthetic steroids, [melengestrol acetate (MGA), medroxyprogesterone acetate (Provera), norgestrel, norethindrone and R 2323] were studied in rats.

Devices were made by adding 5 or 10% by weight of the compound to liquid Silastic (Dow Medical Grade Elastomer 382). The catalyst, stannous octoate, was added and the mixture extruded into polyethylene tubing 1·07 mm i.d. and allowed to cure. The tubing was cut in 8 mm lengths and autoclaved at a temperature that caused the polyethylene sleeve to soften and melt, allowing easy removal of the sterile device from the sleeve. Copper devices were obtained by using 8 mm segments of Tatum T's. Baboon devices were made by filling silastic tubing with crystalline steroids and sealing both ends.

Devices were placed in ether anesthetized cycling Sprague–Dawley rats *via* a dorsolateral incision to expose the upper third of the uterine horn. A small incision was made on the antimesometrial surface, the device dropped in, and the uterus closed with 6–0 silk suture. The skin was closed with 3–0 suture, the animals returned to individual cages and their estrous cycles and mating, when appropriate, were

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followed by daily vaginal lavage. Laparotomies were done *via* a single dorsolateral incision.

Erythrocebus patas, an Old World primate, was chosen for retention and short term release rate studies in subhuman primates. The cervical anatomy of this animal is similar to the human allowing easy insertion and removal of IUD's; however, little is known concerning the reproductive cycle of these animals as they do not have observable menses. Rhesus monkeys and more recently baboons were used to study the effects of steroid releasing IUD's on the menstrual cycle.

Devices were inserted transfundally at laparotomy into anesthetized monkeys or transcervically into tranquilized baboons whose menstrual cycles had been followed for 6–12 months prior to insertion.

Primate cages were searched daily for expelled devices and animals were checked weekly by speculum examination for strings, or by fluoroscopy or X-ray to confirm device location. The menstrual cycle was checked daily in the baboons and rhesus.

Determination of release rates for the various compounds was by weight loss of the device and by determination of the amount of compound left in the device as estimated by extraction and gas chromatographic or spectrophotometric quantitation.

The effect of the compounds on device retention in rats is summarized in Fig. 1. All compounds except copper increased retention; however, as the synthetic progestins were the most effective, only these five were studied extensively. Female rats with active devices in one horn were placed with males and checked daily for the presence of sperm or plug. None of the five compounds at 5% appeared to inhibit mating; however, mated animals did not retain the devices as well as non mated animals (Fig. 2).

Three of the synthetic steroids, (Provera, norgestrel and norethindrone), were at that time approved for human use and as all had shown promise in the

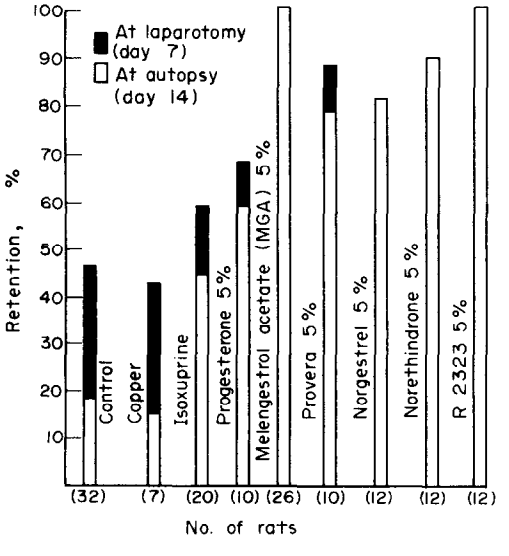

Fig. 1.

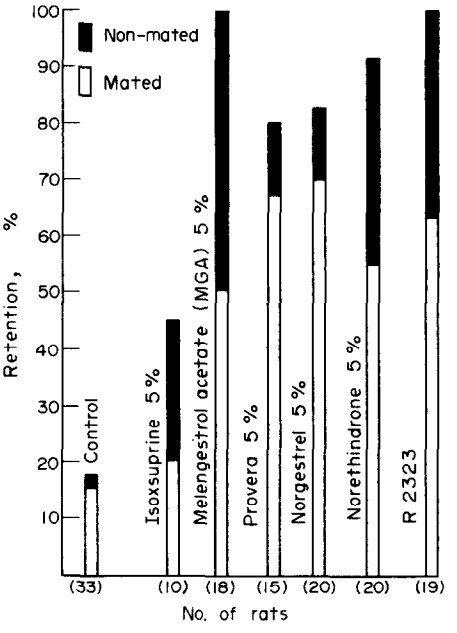

Fig. 2.

rodent retention in mated animals, they were chosen for further studies in primates.

Five control and 16 devices with 10% Provera were inserted into four patas monkeys. Two control devices were expelled as were three of the active devices. Another three of the active devices were not found in the cage, nor could they be visualized by X-ray, so no increased retention could be demonstrated in this species. Of 17 control devices inserted into baboons, only two remained in longer than 28 days and 13/17 were expelled in less than 7 days. Seven devices with Provera have been inserted. Two remained *in situ* 83 days and were then removed for study. Only one was expelled within 1 week, three within 2 weeks and one within 4 weeks. Four norgestrel and 2 norethindrone devices have been inserted into baboons and none were found *in situ* at 7 days. The baboon data are summarized in Table 1.

In the rhesus monkeys, fluctuation in control cycle length, (19–84 days), made statistical analysis impossible; however, mean cycle length tended to increase with Provera IUD's *in utero* and return to control means following removal in the three animals that had devices in 2 months and the three animals in the 4 month study. In contrast, the three animals in the 6 month group show no difference between mean cycle length before or during the experiment.

The two baboons with Provera devices *in situ* for 83 days never demonstrated the perineal swelling associated with ovulation in this species, nor did they exhibit regular menses, despite an occasional day of bleeding. Both animals bled 3 days after the devices were removed. Withdrawal bleeding was seen in rhesus only when the device was removed at 1 month. A third baboon who retained the device at least 21 days had a normal menses 33 days after

Table 1. Retention time for steroid releasing IUD's in baboons

Compound	Total insertions	Number of IUD's retained (days) Less than 7	7–14	21–28	More than 28
Control	17	13 (76·5%)	1 (5·9%)	1 (5·9%)	2 (11·8%)
Provera	7	1 (14·3%)	3 (42·9%)	1 (14·3%)	2 (28·6%)
Norgestrel	4	4 (100%)			
Norethindrone	2	2 (100%)			

her last period of bleeding; however, she had demonstrated no cyclic perineal swelling during this cycle.

Release rates

A comparison between release rates of Provera devices incubated in saline, distilled water, or *in utero* demonstrated no correlation between *in vivo* and *in vitro* release rates as can be seen in Table 2 so all other release rate studies were done in rodents or primates.

Studies done on devices that had been *in situ* for 2 weeks indicated that norgestrel had the slowest release rate, followed by Provera, norethindrone, and R 2323 (Table 3).

The pattern of release from the rods was a short period of equilibration during which a large amount of Provera was released followed by a long period during which a relatively constant amount was released each day (Table 4). After a 2 week period the release/day was in the range of 40 mcg in both patas and rhesus. Despite the fact that a different total dosage and delivery module were used, a release rate in the same range was found in the two baboons whose devices remained *in situ* for 83 days. Release rates for the other steroids are not known as none of the expelled devices have been located.

DISCUSSION

The results from this study would seem to indicate that while we may be on the right road to solving the problems of expulsion and bleeding seen in the IUD users, we have now only taken "one small step for woman" along this road.

Although all of the synthetic steroids demonstrated a marked ability to cause device retention in rats, they do not appear to have this effect in either patas or baboons. Several factors may account for this difference. The amount released from the device in relation to body weight of the animal was much greater in the rodents than in primates so the retention may be dose related. There may well be a species difference in sensitivity to various steroids, or the primate endometrium may either bind or metabolize these progestins so that they are unable to exert an effect on the myometrium. Inability to detect Provera in the peripheral plasma of the patas while finding it in rat sera would tend to favor the latter view that the drug is metabolized by the endometrium; however, the apparent lack of effect on other reproductive parameters in rats but not in primates where menstrual cycle abberations were the rule rather than the exception, would contradict this. A difference in sensitivity to the various synthetics seems to be supported by the fact that while all of the synthetic progestins enhanced retention in rats, only Provera appeared to demonstrate this quality to any degree in primates. A similar effect on retention has been reported in humans [3]. Retention of Provera releasing IUD's in patas and baboons was better than that of controls; however, only two devices remained *in situ* until removal at 83 days.

The amount of Provera being released from either 10% rods containing 1·5 mg or capsules containing approximately 15–16 mg in patas, rhesus, and baboons ranged from 24–43 μg/day after the initial equilibration period. This amount was enough to alter the menstrual cycle in some, but not all, animals of both species. In two rhesus monkeys who had exhibited menses with the device *in situ*, the endometrial biopsy following menses showed decidual changes so amounts of Provera which do not affect the systemic hormones apparently can induce local endometrial alteration. This endometrial effect on cycling animals is similar to that reported by Scommegna *et al.* in humans with progesterone releasing IUD's [4].

The advantages of using a synthetic steroid rather than the natural hormone are multiple. The natural hormone did not cause an increased rate of retention

Table 2. *In vivo* and *in vitro* release rate of provera from 5% IUD's*

Time in study (h)	*In vivo* release (μg/24 h)	*In vitro* release (μg/24 h) Saline	Distilled water
6	65·2 ± 9·0 (5)†	322·9 ± 82·2 (4)	60·5 ± 17·1 (3)
12	64·0 ± 28·5 (5)	116·9 ± 24·4 (5)	52·0 ± 22·1 (5)
24	84·9 ± 34·0 (7)	66·9 ± 18·7 (5)	24·9 ± 17·4 (5)
48	50·4 ± 13·8 (6)	52·4 ± 3·5 (5)	27·9 ± 13·2 (4)

* Average 470 μg provera/device.
† Number of devices.

Table 3. *In vivo* release rates (μg/24h) from 5% steroid IUD's

Steroid*	Number of devices	Time device left in rat 1 week	2 weeks	3 weeks
Provera	4	28·60 ± 0·44		
	5		21·60 ± 0·24	
Norgestrel	15		10·54 ± 0·74	
	5			17·90 ± 1·09
Norethindrone	14		24·78 ± 5·20	
	3			17·60 ± 0·99
R 2323	12		33·61 ± 0·99	
	4			24·55 ± 2·08

* All devices contained approximately 470 mcg.

Table 4. Release of provera in primates

Days in primate	Type primate	Number primates	Total initial dose (μg)	Total released (μg)	Release/day (μg)
2	Patas	4	1500*	435·0	217·5
4	Patas	3	1500*	516·0	129·0
7	Patas	1	1500*	574·5	82·0
16	Patas	2	1500*	694·5	43·4
20	Patas	1	1500*	823·5	41·1
30	Rhesus	2	1500*	1164·0	38·8
60		1	1500*	1140·0	24·0
83	Baboon	2	15,600	2940·0	35·4
			16,400	2900·0	34·9

* Average amount of steroid in 10% Provera devices used in primates.

in our animal studies, nor has it abolished expulsion of devices in humans [5]. Stryker[3] reports no intermenstrual bleeding in her pilot study with Provera releasing IUD's; however, this has not been reported for progesterone IUD's where an 8·3–12·2 incidence of pain and bleeding has been recorded [5]. Even if progesterone were effective in enhancing retention, several other qualities must be considered. It has a shorter biologic half life than synthetic steroids; it generally requires much more of the natural than synthetic steroid to achieve the same biologic end point; and it is released from silastic more quickly than the more polar synthetics [6]. In short, a greater quantity of progesterone would have to be incorporated into the IUD, and when one is dealing with a system where longevity is important, this becomes a critical determinant in choice of drug.

The IUD in these experiments was deliberately designed for poor retention so the steroid effects could be determined. It is possible that the addition of Provera, while not able to make a bad device good, could make an average device excellent. The possibility of other synthetic steroids being useful looks rather dim from the baboon data with norgestrel and norethindrone; however, more data is necessary before these compounds are discarded, and still other synthetic progestins remain to be investigated.

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