Vaginal Absorption of a Potent Luteinizing Hormone-Releasing Hormone Analogue (Leuprolide) in Rats IV: Evaluation of the Vaginal Absorption and Gonadotropin Responses by Radioimmunoassay

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Abstract □ The vaginal absorption of leuprolide (a potent luteinizing hormone-releasing hormone analogue), which has the potential for producing regression of hormone-dependent tumors as well as high gonadotropin-releasing and ovulation-inducing activities, was evaluated in rats by radioimmunoassay. Gonadotropin (luteinizing hormone and follicle-stimulating hormone) release was concomitantly determined. Although leuprolide disappeared rapidly from the serum after intravenous administration (the biological half-lives were 8.4 min in the α-phase and 33.2 min in the β-phase), long-lasting serum levels were observed when the analogue was administered vaginally. The vaginal absorption was enhanced by adding citric acid to the test solution. The absolute bioavailability, estimated by the AUC of serum leuprolide levels, was 25.8% over 6 h and 38.0% over 12 h in the 5% citric acid solution (pH 3.5). The sustained release of gonadotropin was also obtained after vaginal administration of the analogue. A linear dose absorption correlation of leuprolide was obtained in the range of 10–1000 μg/kg in an aqueous solution or methylcellulose jelly. The release of gonadotropin showed a plateau level at >10 μg/kg, which corresponds to an effective dose for antitumor activity. The vaginal absorption of leuprolide varied with the estrous cycle, but this effect was eliminated by prior subcutaneous pretreatment with the analogue.

Keyphrases □ Leuprolide—vaginal absorption in rats, gonadotropin responses, effect of the estrous cycle, radioimmunoassay □ Gonadotropin response—leuprolide in rats, vaginal absorption, effect of the estrous cycle, radioimmunoassay □ Estrous cycle—effect on the vaginal absorption of leuprolide in rats, gonadotropin responses, radioimmunoassay

Leuprolide (I), a potent luteinizing hormone-releasing hormone (II) analogue (desGly^{10}-D-Leu^{6}-II ethylamide), has high gonadotropin-releasing and ovulation-inducing activities (1, 2). Recently, multiple high doses of leuprolide were found to effect regression of hormone-dependent mammary tumors (3, 4) and to have birth control potential in both sexes (5–8).

In our previous studies (9–11), investigations were conducted on the various routes of leuprolide administration for long-term therapy or convenient self-administration and on the absorption enhancement by assessing the ovulation-inducing activity in rats. We found that vaginal absorption was good and was enhanced by adding organic acids such as citric or succinic acid to the test solution. Although the estrous cycle influenced the vaginal absorption of phenolsulfonphthalein and insulin (used as hydrophilic markers), this influence was eliminated by a consecutive daily subcutaneous pretreatment with the analogue. Thus, the vaginal application of leuprolide was proposed as a practical route for long-term usage.

In the present study, we used a newly developed radioimmunoassay (RIA) for leuprolide (12) to investigate the pharmacokinetics of the analogue after intravenous administration, vaginal absorption, absorption enhancement, dose–absorption correlation, and the effect of the estrous cycle on vaginal absorption. Gonadotropin [luteinizing hormone (III) and follicle-stimulating hormone (IV)] release after vaginal administration of leuprolide was also determined by the RIA.

EXPERIMENTAL

Animals and Materials—Mature female Sprague–Dawley rats[1], 120–150 d of age, 250–330 g, which exhibited two or more consecutive 4-d estrous cycles were used. Leuprolide was administered to rats in the morning during the diestrus, except when studying the effect of the estrous cycle. Leuprolide was prepared as described previously (2) and was dried at 50°C under vacuum for 5 h before use. The analogue contained 6.2% acetic acid (as salt) and 2.5% water.

Radioimmunoassay of Leuprolide and Gonadotropin—Serum levels of leuprolide were determined in duplicate by the double-antibody RIA method reported previously (12). The serum sample or standard solution (0.2 mL) was mixed with 0.4 mL of 1% bovine serum albumin[2]–0.01 M phosphate-buffered saline (pH 7.0), 0.2 mL of rabbit anti-leuprolide serum diluted 1:10,000 in 1% bovine serum albumin–phosphate-buffered saline (pH 7.0) containing 0.05 M EDTA, and 0.1 mL of [^{131}I]leuprolide in 0.1% bovine serum albumin–phosphate-buffered saline (pH 7.0). After 48 h of incubation at 4°C, 0.2 mL of an appropriate dilution of goat anti-rabbit γ-globulin serum[3] (0.05 mL) and normal rabbit serum[3] (0.15 mL) in the buffered saline solution was added to each tube and the contents were mixed. Following an additional 24-h incubation at 4°C, the tube was centrifuged at 1000×g for 30 min, the supernatant aspirated, and the precipitate counted in an automatic gamma-counter[4].

Iodination of leuprolide was performed by the lactoperoxidase method (13). [^{131}I]Leuprolide was purified by gel filtration[5] with 0.2 M acetic acid as eluant. The specificity, sensitivity, and accuracy of the RIA for leuprolide have been described and characterized previously (12). The minimum measurable amount of the analogue using the antiserum was ~5 pg/tube (range: 5–10,000 pg/tube); the CV was <11.2% (50–1000 pg/tube) intra-assay and <19.2% (50–1000 pg/tube) interassay.

Gonadotropins (III and IV) in rat sera were also determined in duplicate by double-antibody RIA (14, 15) using kits[6]. Values are expressed in terms of the standard rat gonadotropins, NIAMDD-Rat-LH (RP-1) and NIAMDD-Rat-FSH (RP-1). The measurable range of both gonadotropins in this system was 1–800 ng/tube. The serum samples, stored at −20°C until assayed, were diluted to an adequate concentration with 0.01 M phosphate buffer (pH 7.0) before the assay.

Intravenous, Subcutaneous, and Vaginal Administration—Leuprolide was administered in the morning intravenously (100 μg/kg/0.1 mL of physiological saline), subcutaneously (100 μg/kg/0.1 mL of saline), and vaginally (500 μg/kg/0.2 mL) to diestrous rats under pentobarbital (50 mg/kg ip) and phenobarbital (100 mg/kg ip) anesthesia. For vaginal administration, leuprolide was dissolved in 5% citric acid solution at pH 3.5 (Solution A) and administered with a cotton ball (~12 mg) using a glass inserter (5-mm o.d.). After administration, the orifice of the vagina

[1] Clea Japan, Inc., Tokyo, Japan.
[2] Wako Pure Chemical Ind., Ltd., Osaka, Japan.
[3] Daiichi Radioisotope Laboratories, Ltd., Tokyo, Japan.
[4] Aloka Auto Well Gamma System, JDC-752; Aloka Co., Ltd., Tokyo, Japan.
[5] Sephadex G-10; Pharmacia Fine Chemicals AB, Uppsala, Sweden.
[6] Supplied by the National Institute of Arthritis, Metabolic, and Digestive Diseases, National Institutes of Health, Bethesda, Md.

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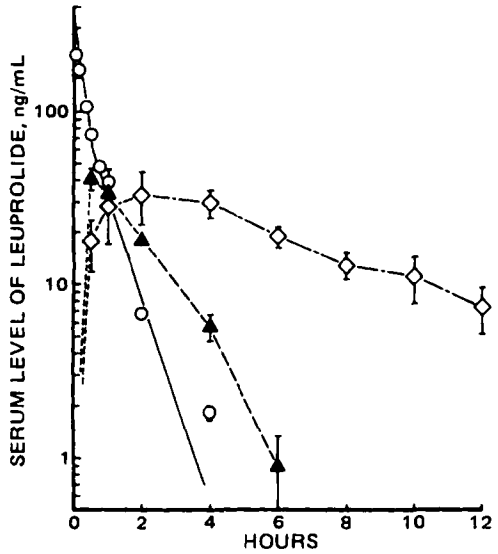

Figure 1—*Serum levels (log scale) of leuprolide after intravenous (○), subcutaneous (▲), and vaginal (◇) administration to diestrous rats. The analogue was administered intraveneously and subcutaneously at a dose of 100 μg/kg/mL in saline, and vaginally at 500μg/kg/0.2 mL in solution A, 5% citric acid solution (pH 3.5). Each point represents the mean ± SE of three or five (vaginal) rats.*

was sealed with a surgical adhesive agent. Blood (~0.5 mL) was collected from the tail vein at appropriate times during 12 h, and the serum was stored until assayed. In cases of intravenous administration, a group of three rats was used for blood collections (0.2–0.5 mL) at 5, 20, 45, 120, and 360 min postadministration and another group was used for collections at 10, 30, 60, and 240 min to prevent physiologically abnormal conditions (hypovolemia).

The pharmacokinetic parameters were obtained by fitting the individual rat data during 6 h to a two-compartment open model *via* the nonlinear least-squares regression computer program NONLIN (16). The

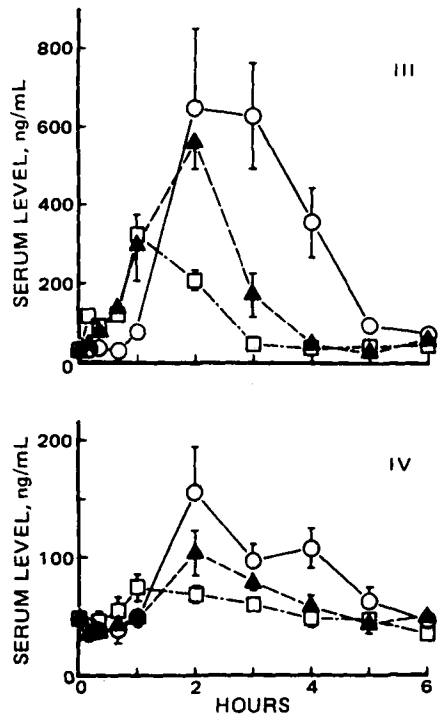

Figure 2—*Serum gonadotropin levels after intravenous (□), subcutaneous (▲), and vaginal (○) administration of leuprolide to diestrous rats. The analogue was administered at a dose corresponding to the ED_{50} of ovulation-inducing activity (38 ng/kg iv, 58 ng/kg sc, and 99 ng/kg) in 5% citric acid solution (pH 1.8) vaginally. Each point represents the mean ± SE of five rats.*

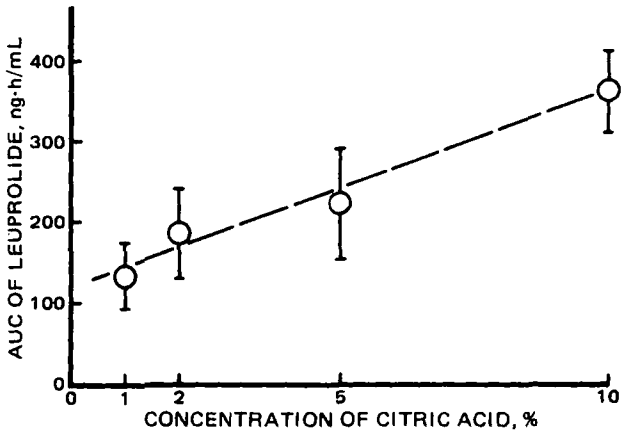

Figure 3—*AUC of leuprolide over 6 h after vaginal administration in the pH 3.5 aqueous solutions containing different concentrations of citric acid to diestrous rats. Dose of the analogue was 500 μg/kg/0.2 mL in the acid solution. Each point represents the mean ± SE of five rats.*

area under the serum level–time curve (AUC) of leuprolide was calculated by a trapezoidal method within the last collected time value, and the bioavailability was obtained using:

$$\text{Bioavailability (\%)} = \frac{AUC^{t}_{0,vag} \text{ or } AUC^{t}_{0,sc}}{AUC^{t}_{0,iv}} \times 100 \qquad \text{(Eq. 1)}$$

where t is the last collection time.

Gonadotropin release was determined after intravenous, subcutaneous, and vaginal administration of leuprolide at the dose corresponding to the ED_{50} of the ovulation-inducing activity [38, 58, and 99 ng/kg, respectively (9, 10)] in unanesthetized rats at diestrus. The analogue was dissolved in physiological saline containing 0.1% bovine serum albumin, 20 U/mL of aprotinin[7], and 0.01 M HCl for intravenous and subcutaneous administration, and in 5% citric acid solution (pH 1.8) for vaginal administration. Whole blood was taken from the abdominal aorta with the rats under ether anesthesia 10, 20, 40, 60, 120, 180, 240, 300, and 360 min after administration.

Enhancement of Vaginal Absorption—Aqueous solutions of leuprolide (500 μg/kg/0.2 mL) containing four different concentrations of citric acid were administered vaginally (cotton ball technique) to anesthetized diestrous rats. Each solution was previously adjusted to pH 3.5 by 10 M NaOH and 2 M HCl and to an isotonic preparation with sodium chloride. Blood was collected from the tail vein to determine the serum levels of leuprolide.

Dose-Absorption and Response Correlations—Four different doses (10–1000 μg/kg) of leuprolide in Solution A or 5% methylcellulose[8] jelly

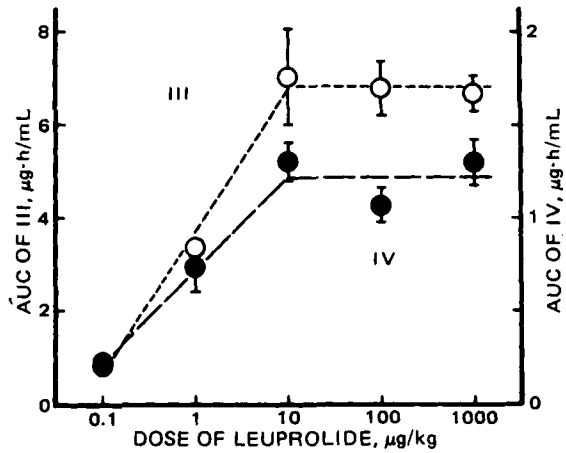

Figure 4—*Dose response (AUC of serum gonadotropin levels over 6 h) curves after vaginal administration of leuprolide to diestrous rats. The analogue was dissolved in solution A and administered at a dose of 0.1, 1, 10, 100 μg, and 1 mg/kg. Each point represents the mean ± SE of five rats.*

[7] Trasylol; Bayer AG, Leverkusen-Bayerwerk, W. Germany.
[8] Metolose 90SH4000; Shinetsu Chemicals Co., Tokyo, Japan.

Table I—AUC of Leuprolide after Vaginal Administration in Solution A[a] or 5% Methylcellulose Jelly Containing Solution A to Diestrous Rats

Dose, μg/kg	AUC of Leuprolide, ng·h/mL[b]	
	Aqueous Solution	Jelly
10	3.75 ± 0.82	—
50	19.3 ± 4.66	12.8 ± 1.56
100	34.6 ± 10.6	38.0 ± 7.43
500	222.0 ± 68.8	166.5 ± 19.1
1000	—	408.3 ± 33.7

[a] 5% citric acid solution, pH 3.5. [b] AUC was calculated from 0 to 6 h; each value represents the mean ± *SE* of five rats.

containing Solution A were administered vaginally to anesthetized diestrous rats to assay the serum levels of the analogue. Leuprolide was also administered vaginally at a dose range of 0.1–1000 μg/kg/0.2 mL in Solution A, and serum levels of gonadotropin were determined.

Effect of the Estrous Cycle—Leuprolide was administered vaginally at a dose of 500 μg/kg/0.2 mL in Solution A to proestrous, estrous, metestrous and diestrous rats under anesthesia, and the serum level of the analogue was determined. To determine the gonadotropin-releasing responses, an oleaginous suppository[9] containing 100 ng of leuprolide and 10% citric acid was administered vaginally to anesthetized rats exhibiting the four different stages of the estrous cycle.

For the determination of the effect of prior pretreatment of leuprolide on the vaginal absorption, 100 μg/kg of the analogue was given subcutaneously daily for 10 d to rats initially exhibiting the four different stages. The following morning, each rat received a single vaginal administration of 500 μg/kg of leuprolide in Solution A, and the serum levels of the analogue were assayed. Vaginal smears during the subcutaneous administration were examined daily to determine the change of the estrous cycle. The vagina and ovaries were removed for histological examination after taking the 6-h-blood samples.

RESULTS

Intravenous, Subcutaneous, and Vaginal Administration—Serum levels of leuprolide after intravenous, subcutaneous, and vaginal administration to diestrous female rats are shown in Fig. 1.

The pharmacokinetic parameters after intravenous administration were obtained by simulating to a two-compartment open model; the serum level (C_t) at time t was expressed by:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 2)}$$

with A = 241.5 ± 99.6 ng/mL, B = 122.4 ± 43.1 ng/mL, α = 8.37 ± 4.12 h^{-1}, and β = 1.35 ± 0.23 hr^{-1}. Leuprolide rapidly disappeared from the serum: the half-lives were 8.4 ± 4.0 min in the α-phase and 33.2 ± 6.8 min in the β-phase. The transfer rate constants between central and tissue compartments were 2.99 ± 2.32 h^{-1} (from central to tissue) and 3.79 ± 1.35 h^{-1} (from tissue to central). The elimination rate constant from the central compartment was 2.94 ± 0.92 h^{-1}, and the volumes of distribution were 0.32 ± 0.07 L/kg for the central compartment and 1.31 ± 0.71 L/kg for the tissue compartment. Each value represents the mean ± *SE* of three rats.

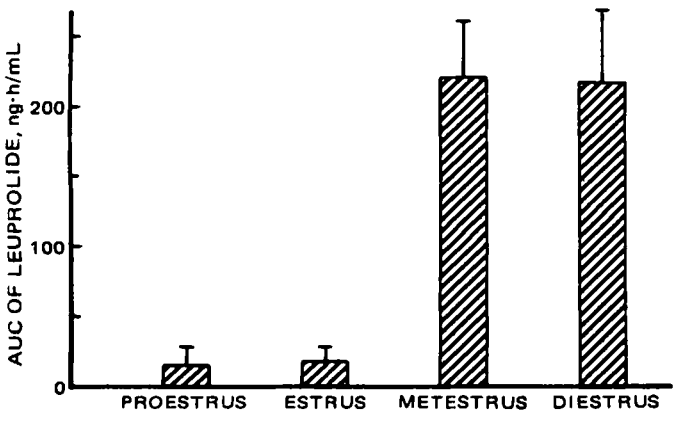

Figure 5—*AUC of leuprolide over 6 h after vaginal administration during different stages of the estrous cycle in rats. Dose of the analogue was 500 μg/kg/0.2 mL in solution A. Each bar represents the mean ± SE of five rats.*

[9] Witepsol S55; Dynamit Nobel Aktiengesellshaft, W. Germany.

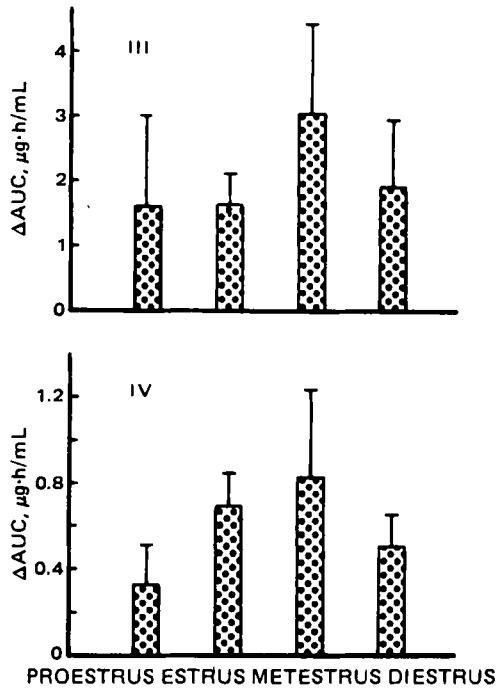

Figure 6—*AUC increment (ΔAUC) of serum gonadotropin levels over 6 h after vaginal administration of leuprolide during different stages of the estrous cycle in rats. The analogue was administered at a dose of 100 ng/rat in an oleaginous suppository containing 10% citric acid. Each bar represents the mean ± SE of three rats.*

The subcutaneous administration resulted in a sustained serum level: the serum level at 4 h after the administration was 3 times higher than that after the intravenous administration. The absolute bioavailability, determined by the AUC over 6 h, was 68.1%. In the case of vaginal administration, leuprolide was absorbed rapidly, and a long-lasting serum level was observed. The maximum serum level was observed 2 h after administration, but values were high and relatively constant over the 6-h period. The absolute bioavailability was 25.8% over 6 h and 38.0% over 12 h.

Gonadotropin-releasing responses to the analogue given by the three routes at doses corresponding to the ED_{50} of ovulation-inducing activity are shown in Fig. 2. The peak times of serum gonadotropin levels were the shortest after intravenous administration, whereas the serum levels after vaginal administration were the highest and had the longest duration. The total release of gonadotropin (which can be represented by the AUC values) after administration of leuprolide by the three routes were directly proportional to the doses given.

Enhancement of the Vaginal Absorption—Serum leuprolide levels after vaginal administration with four different concentrations of citric acid were determined, and the AUC over 6 h is shown in Fig. 3. The AUC increased progressively with the addition of citric acid up to 10%. The absolute bioavailability was 36.0% in the 5% citric acid solution and 58.7% in the 10% solution, which was 2.7 times larger than that in the 1% solution.

Dose Absorption and Response Correlations—Serum leuprolide levels after vaginal administration in either an aqueous solution or a methylcellulose jelly, both containing 5% citric acid, were determined at the dose range of 10–1000 μg/kg, and the AUC values were calculated (Table I). AUC values of serum gonadotropin levels after vaginal administration of leuprolide in Solution A are shown in Fig. 4. A linear relationship between the dose and AUC of leuprolide was observed over the entire range, whereas for the gonadotropin-releasing responses, a linear dose–response correlation was obtained only in the dose range of 0.1–10 μg/kg with a plateau at >10 μg/kg.

Effect of the Estrous Cycle—The AUC (mean ± *SE*) of leuprolide over 6 h after vaginal administration was 15.5 ± 13.0 ng·h/mL during proestrus, 17.4 ± 9.68 ng·h/mL during estrus, 221.3 ± 42.2 ng·h/mL during metestrus, and 218.8 ± 60.8 ng·h/mL during diestrus (Fig. 5). The AUC

values during metestrus and diestrus were 13 times higher than those during proestrus and estrus.

Gonadotropin release after vaginal administration of leuprolide during the four different stages of the cycle showed large variation, and the effect was not so clear as that seen for serum levels of the analogue (Fig. 6). However, the AUC increments of serum gonadotropin levels during metestrus and diestrus were larger than those seen during proestrus and estrus. The serum level of IV at estrus before vaginal administration was twice that seen at the other stages.

Vaginal absorption of leuprolide in rats pretreated with daily subcutaneous administrations of the analogue for 10 d was rapid and of increased magnitude; the maximum serum levels obtained between 1 and 2 h after vaginal administration were ~3 times larger than those in nontreated diestrous rats. The AUC values (mean ± *SE*) over 6 h after vaginal administration were 577.9 ± 59.0 ng·h/mL for proestrus (of the initial stage before cycle was disrupted due to the subcutaneous pretreatment), 530.4 ± 119.6 ng·h/mL for estrus, 571.0 ± 49.5 ng·h/mL for metestrus, and 550.0 ± 6.4 ng·h/mL for diestrus, respectively (Fig. 7).

Despite initiation of the pretreatment at different stages of the estrous cycle, the AUC values of leuprolide showed small fluctuations and were 2.5 times larger than that in nonpretreated diestrous rats. The examination of vaginal smears revealed that the estrous cycle was halted at diestrus in all rats as a result of subcutaneous pretreatment with the analogue. The histological observation after this experiment showed a thinner vaginal epithelium than that seen at normal diestrus, infiltration of neutrophil leucocytes in the vagina, and an increase in the number of corpora lutea with no Graafian follicles in the ovaries.

DISCUSSION

The disappearance of leuprolide from the serum of rats after intravenous administration was rapid; the biological half-lives were 8.4 min in the α-phase and 33.2 min in the β-phase. The half-life in the α-phase was identical to that of [^{3}H]II in female (17) and male rats (18). This result supports the idea that the potent and long-lasting activity of leuprolide is due not to the slow disappearance from the circulation, but rather to the high uptake in the anterior pituitary (19) or to a high receptor-binding affinity (20). The serum level of the analogue after subcutaneous administration was maintained for a longer period than that after intravenous administration, and the absolute bioavailability was 68.1%. After vaginal administration, high and long-lasting serum levels of leuprolide were observed with the absolute bioavailability up to 6 h being 25.8%. Although the true availability should be estimated to be much larger when sampling blood for a longer period, the bioavailability over 6 h paralleled the case of ovulation-inducing activity (10).

Gonadotropin release after leuprolide administration by the three routes, which was evaluated at the lowest dose exhibiting a linear dose–response correlation, was not identical, despite using doses corresponding to the ED_{50} of the ovulation-inducing activity. The different responses are possibly due to the lag time of distribution to the target organ (anterior pituitary), the releasing balance of gonadotropins III and IV, hormonal feedback, and sensitivity of the target cells. Nevertheless, these results do indicate that the vaginal absorption of leuprolide resulted in a maintenance of high serum levels and pituitary responses.

In our previous studies (9, 10) we demonstrated, by the determination of ovulation-inducing activity, that citric acid enhanced the vaginal absorption of leuprolide. In this study, it was directly confirmed that the acid progressively enhanced the vaginal absorption of the analogue at the concentrations used (Fig. 3).

Linear correlations between dose and vaginal absorption of leuprolide in an aqueous solution and methylcellulose jelly (as a practical dosage form) were obtained by determining the serum level of the analogue (Table I). However, both gonadotropin-releasing responses were proportional to the dose within 0.1–10 μg/kg and showed a plateau between 10–1000 μg/kg. Such saturation of the gonadotropin-releasing response at higher doses of II and its analogues has been reported (21–23) and is possibly due to the negative feedback effect of estrogen (24–26) or to the decrease of gonadotropin-releasing hormone receptor cells in the pituitary ("down regulation") (27–29). On the other hand, the minimum effective dose of leuprolide to produce regression of rat mammary tumors induced by 7,12-dimethylbenz[*a*]anthracene was ~100 μg/kg by vaginal administration[10], which is well within the dose range that caused a maximum pituitary stimulation in the present study.

In a previous study, we found that the estrous cycle of rats affected the vaginal absorption of insulin and phenolsulfonphthalein, used as markers

[10] Unpublished data.

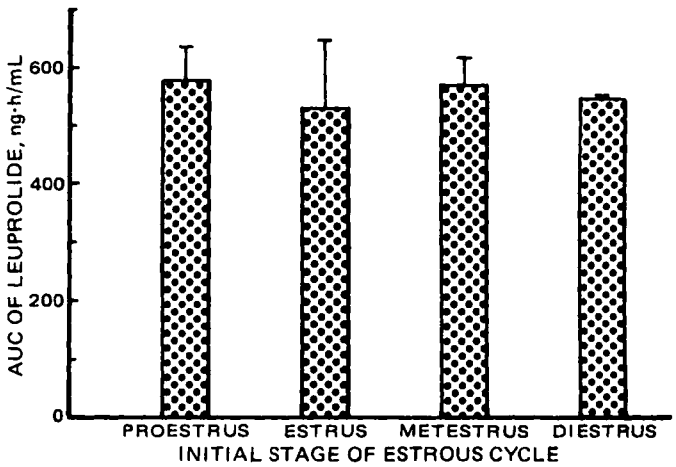

Figure 7—*AUC of leuprolide over 6 h after vaginal administration. Rats were pretreated subcutaneously with the analogue at a dose of 100 μg/kg/d for 10 d followed by a single vaginal dose of 500 μg/kg in solution A. Each bar represents the mean* ± SE *of three rats.*

of hydrophilic compounds (11). The vaginal absorption of leuprolide also was affected by the estrous cycle to the same degree as seen with phenolsulfonphthalein; the vaginal absorption during metestrus and diestrus was 13 times greater than that during proestrus and estrus. The effect of the estrous cycle can be explained by the change of pore-like pathways in the vaginal epithelium (11, 30), producing an unavoidable fluctuation in the vaginal absorption of drugs.

Gonadotropin release after vaginal administration of leuprolide throughout the estrous cycle has not been shown to be clearly dependent on the cycle, as is the case with the serum level of the analogue; high serum levels of gonadotropin were observed even during proestrus and estrus. This phenomenon is ascribed to increased absorbability due to alteration of the vaginal epithelium and to the pituitary responsiveness due to feed-back by progestins and estrogens (31–34) or due to regulation of gonadotropin-releasing hormone receptors (29, 35) during the estrous cycle. The responsiveness of III and IV to leuprolide is the highest at proestrus and estrus, respectively (36–38). Furthermore, the spontaneous surge is provoked in the afternoon of proestrus for III, and from the afternoon of proestrus to the morning of estrus for IV (35, 39). Nevertheless, the high serum levels of gonadotropin during metestrus and diestrus (with the lower pituitary responsiveness) should support the good vaginal absorption of the analogue.

Undue influence of the estrous cycle on the absorption of drugs is unfavorable for effective vaginal application. However, in the case of leuprolide, the pretreatment administration halted the cycle at diestrus, and resulted in a good vaginal absorption of the analogue with less variation. The augmented absorption compared with that in nonpretreated diestrous rats may be attributed to the thinner epithelium of the vagina, as seen histologically. Likewise, the enhancement of vaginal absorption of a hydrophilic marker compound by pretreatment with leuprolide was demonstrated in our previous study (11); cessation of the cycling at diestrus was also demonstrated by the vaginal smear examination and by histological observations.

In summary, leuprolide was absorbed sufficiently through the vagina in diestrous rats; prolonged serum levels of the radioimmunoreactive analogue and potent gonadotropin-releasing responses were observed, and the vaginal absorption of the analogue was enhanced by adding citric acid. Modifying effects of the estrous cycle on the vaginal absorption were observed, but such variations were eliminated by prior parenteral pretreatment with the analogue. From these results, we conclude that vaginal application of leuprolide can be a potentially effective method as self-administration or long-term treatment for anticancer or fertility control. Moreover, we propose that vaginal application of leuprolide be performed as a maintenance dose following consecutive parenteral administration, in order to terminate the menstrual cycle and provide a vaginal environment conducive to maximal analogue absorption with less variation.

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In Vitro Release of Salicylic Acid from Lanolin Alcohols–Ethylcellulose Films

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Abstract □ Lanolin alcohols–ethylcellulose films were investigated as a potential drug delivery system for the controlled release of salicylic acid. The effects of changes in film composition, drug concentration, drug solubility, and stirrer speed on the *in vitro* release of salicylic acid have been examined. The drug release has been found to obey a diffusion-controlled matrix model and square root of time release profile both in the suspension and solution cases.

Keyphrases □ Salicylic acid—*in vitro* release from lanolin alcohols–ethylcellulose films, drug diffusion □ Lanolin alcohols—films with ethyl cellulose, *in vitro* release of salicylic acid, drug diffusion □ Ethylcellulose—films with lanolin alcohols, *in vitro* release of salicylic acid, drug diffusion □ Drug diffusion—*in vitro* release of salicylic acid from lanolin alcohols–ethylcellulose films

The film-forming potential of nonpolymeric materials such as lanolin alcohols, which are extensively used in cosmetic and pharmaceutical formulations, has been recently investigated in our laboratory (1). Lanolin alcohols were found to form isolatable thin films on a mercury substrate. The incorporation of small percentages of ethylcellulose, a known film former (2), and a plasticizer such as propylene glycol with lanolin alcohols was found to give tack-free films of improved quality.

Effective utilization of nonpolymeric substances such as lanolin alcohols in film-forming composition holds considerable promise for a variety of reasons. Such delivery systems could be designed and formulated to provide sustained drug delivery. The potential hazards associated with monomeric impurities in polymers are avoided. Nonpolymeric materials are easy to manipulate and compound, and are relatively easy to obtain in a state of definable composition. They also can be washed from the skin with relative ease using soap and water.

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