formulations such as those made from polymers III or IV would be expected to provide greater wash resistance than the I–silicone formulations. In tests on human subjects, acrylate formulations such as 25, but not silicone formulations, enhanced I wash resistance (4). However, the contact angles would not necessarily reflect a difference in wash resistance due to a difference in film adhesion to the skin or a difference between a solid flexible film and a liquid film with similar contact angles.

In a preliminary test on hairless dogs, only one of the I formulations (28) appeared to provide greater duration of protection against *A. aegypti* mosquitoes than unformulated I. Results obtained by the ED_{50} and 4-hr test methods were more promising. The ED_{50} of the test repellent was significantly enhanced in two of the seven repellent–acrylate polymer formulations and in three of the eight repellent–silicone polymer formulations (Tables VI and VII). The 4-hr ED_{50}, which measures the combined effects of repellency and persistence on the skin of the test animal, was enhanced significantly in three of the seven repellent–acrylate polymer formulations and in three of the eight repellent–silicone polymer formulations (Tables VIII and IX). Both ED_{50} and 4-hr ED_{50} were enhanced in only one formulation (16, Tables VII and IX). This demonstrates that repellency and persistence on the skin are fundamentally different properties of the repellent formulation. As has been pointed out (12), these two properties of topical repellents have usually been confounded in the past.

In future studies with mosquito repellent formulations, the release kinetics of the repellent (either to evaporation or penetration) will be examined using an *in vitro* skin evaporation–penetration apparatus. Additional knowledge will permit more than an empirical approach to the design of longer lasting mosquito repellent formulations.

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Vaginal Absorption of a Potent Luteinizing Hormone–Releasing Hormone Analogue (Leuprolide) in Rats III: Effect of Estrous Cycle on Vaginal Absorption of Hydrophilic Model Compounds

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Received February 2, 1982, from the *Central Research Division, Takeda Chemical Industries, Ltd., 2-17-85 Juso, Yodogawa, Osaka 532, Japan.* Accepted for publication April 1, 1982.

Abstract □ The effect of estrous cycle stages on vaginal absorption was determined by the use of insulin, phenolsulfonphthalein, and salicylic acid as hydrophilic model compounds. Absorption of these compounds was markedly affected by the stage, possibly due to the change of transport rate through the pore-like pathways. The absorption of phenolsulfonphthalein during proestrus and estrus is roughly one-tenth of that during metestrus and diestrus. An increase of the nonionized form of salicylic acid, produced by a lowered pH, resulted in an enhancement of absorption during proestrus and diestrus; higher contribution of the transport through the cell membrane possibly reduced an effect of the estrous cycle. However, consecutive daily administration of leuprolide halted the cycle at diestrus and reduced the cycle effect on the vaginal absorption of phenolsulfonphthalein; when the treatment was started at any of the four stages of the cycle, vaginal absorption was enhanced ~20%, with less variance than that observed in normal diestrous rats.

Keyphrases □ Absorption, vaginal—luteinizing hormone–releasing hormone, leuprolide, effect of estrous cycle on vaginal absorption of hydrophilic model compounds □ Leuprolide—effect of estrous cycle on vaginal absorption of hydrophilic model compounds □ Luteinizing hormone–releasing hormone analogue—effect of estrous cycle on vaginal absorption of hydrophilic model compounds □ Releasing hormone analogue—luteinizing hormone, effect of estrous cycle on vaginal absorption of hydrophilic model compounds

In previous studies (1, 2), vaginal application was proposed as a rational dosage method for long-term self-administration of hydrophilic drugs, because leuprolide (I), a potent luteinizing hormone–releasing hormone (II) analogue, and several hydrophilic compounds (phenolsulfonphthalein, insulin, and II) are well absorbed through the vaginal membrane of diestrous rats.

(Pyro)Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NH-CH_2CH_3

I

(Pyro)Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2

II

In those studies, vaginal absorbability was estimated at the diestrus only, since the ovulation-inducing activity of leuprolide could be examined during other stages.

The estrous cycle of the rat is completed in 4–5 days, and during this cycle changes in the vaginal mucosal membrane, the ovaries, and the uterus occur (3). Similar, but not as remarkable, changes of the vaginal mucosa occur in women during the menstrual cycle (4).

In the present study, the effect of estrous cycle stages on vaginal absorption was determined with phenolsulfonphthalein, insulin, and salicylic acid in rats. Furthermore, as continuous administration of leuprolide halts the estrous cycle of rats at diestrus (5), the vaginal absorption of phenolsulfonphthalein following consecutive subcutaneous injection of the analogue over a 10-day period was also estimated.

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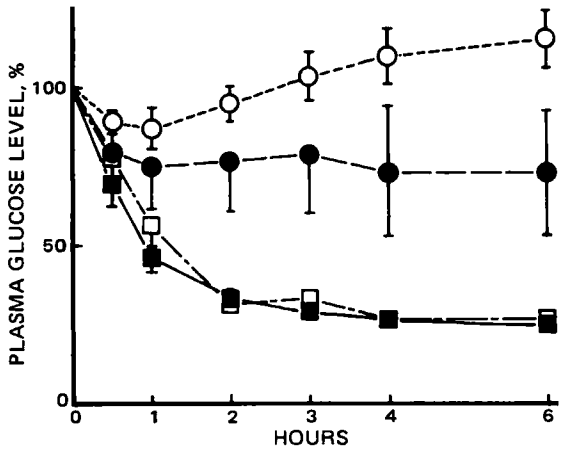

Figure 1—*Plasma glucose levels after vaginal administration of insulin during different stages of the estrous cycle in rats. Insulin was administered vaginally at a dose of 20 U/rat in an oleaginous suppository containing 10% citric acid. The glucose level is shown as a percentage against the initial level. Each point represents the mean ± SE of five rats. Key: (○) proestrus; (●) estrus; (□) metestrus; (■) diestrus.*

EXPERIMENTAL

Animals and Materials—Mature female Sprague-Dawley rats[1] (age, 120–150 days; weighing 250–330 g) exhibiting two or more consecutive 4-day estrous cycles were used.

Leuprolide and insulin were of the same quality used previously (1, 2), and the other chemicals were of reagent grade.

Effect of Estrous Cycle on Vaginal Absorption of Insulin and Phenolsulfonphthalein—Twenty units of porcine insulin (26.29 U/mg) in an oleaginous base[2] containing 10% citric acid was administered vaginally to proestrous, estrous, metestrous, and diestrous rats under pentobarbital (50 mg/kg) and phenobarbital (100 mg/kg) anesthesia. Blood was collected from the tail vein 0.5, 1, 2, 3, 4, and 6 hr after the administration, and 30 μl of the plasma was used for the assay of glucose levels (2).

Phenolsulfonphthalein was administered vaginally at a dose of 2 mg/kg/0.2 ml in pH 6.68, 0.03 *M* phosphate buffer solution (isotonic) to rats exhibiting the four different stages of the estrous cycle. Phenolsulfonphthalein in the urine collected for 6 hr by cannula was determined (2).

Vaginal Absorption of Salicylic Acid at Various pHs in Diestrous and Proestrous Rats—Salicylic acid dissolved at 1% in 0.2 *M* phthalate–hydrochloric acid buffer (pH 3.49), 0.2 *M* phthalate–sodium hydroxide buffer (pH 4.08 and 4.80), 0.1 *M* glycine–hydrochloric acid buffer (pH 3.53 and 4.53), and 0.03 *M* phosphate buffer (pH 5.73), and at 0.4% in 0.2 *M* potassium chloride–hydrochloric acid buffer (pH 2.29), was

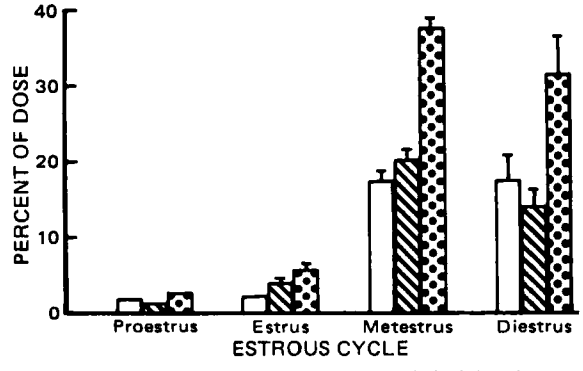

Figure 2—*Urinary excretion of phenolsulfonphthalein after vaginal administration at different stages of the estrous cycle in rats. Phenolsulfonphthalein was administered at a dose of 2 mg/kg/0.2 ml in the pH 6.68 phosphate buffer solution. Each bar represents the mean ± SE of five rats. Key: (□) 0–3 hr; (▨) 3–6 hr; (□) total.*

[1] Clea Japan, Inc., Tokyo, Japan.
[2] Witepsol S55, Dynamit Nobel Aktiengesellschaft, West Germany.

Table I—Remaining Percentage of Salicylic Acid [a] 1 hr after Vaginal Administration in Various pH Solutions to Diestrous and Proestrous Rats

$pH_{observed}$ (buffer)	Diestrus	Proestrus
2.29 (KCl–HCl)	7.1(1.5)[b]	10.4(2.5)
3.49 (phthalate)	18.2(2.1)	28.9(10.0)
3.53 (glycine)	44.0(1.8)	80.7(0.7)
4.08 (phthalate)	32.0(2.8)	58.3(2.9)
4.53 (glycine)	55.8(5.2)	82.1(11.4)
4.80 (phthalate)	35.2(2.1)	71.4(1.1)
5.73 (phosphate)	32.1(3.5)	71.3(12.2)

[a] Salicylic acid was administered at a dose of 2 mg/kg/0.2 ml, except at pH 2.29 (0.8 mg/kg/0.2 ml). [b] Each value represents the mean ± *SE* of three rats.

administered vaginally at a dose of 0.2 ml/kg with cotton balls to diestrous and proestrous rats under anesthesia. Each solution was adjusted to be isotonic with sodium chloride. Rats were decapitated 1 hr after administration, and the salicylic acid remaining in the vaginal tract was determined by a modified method (6). The vaginal tract was homogenized[3] in 5 ml of 0.9% NaCl solution and extracted with 8 ml of ethylene dichloride after acidification by the addition of 1 ml of 6 *N* HCl. Six milliliters of the organic layer was re-extracted with 4 ml of iron reagent [0.05% $Fe(NO_3)_3$–0.0035 *N* HNO_3 solution]. Absorbance of the aqueous layer was determined spectrophotometrically at 530 nm.

Vaginal Absorption of Phenolsulfonphthalein after Consecutive Subcutaneous Injection of Leuprolide—Leuprolide (100 μg/kg) was administered subcutaneously once a day for 10 consecutive days to rats exhibiting four different stages of estrous cycle on the initial day, and the vaginal smear was examined during administration. Phenolsulfonphthalein was administered vaginally at a dose of 2 mg/kg/0.2 ml in 5% citric acid solution (pH 3.5) with cotton balls to the pretreated animals, and the urinary excretion was determined (2).

RESULTS

Effect of Estrous Cycle on Vaginal Absorption of Insulin and Phenolsulfonphthalein—The plasma levels of glucose after vaginal administration of insulin to rats at different stages of the estrous cycle are shown as a percentage against the initial level (100%) in Fig. 1. A slight decrease of glucose level was observed only at an early period during proestrus; whereas, a distinct decrease was obtained during estrus and a more remarkable decrease during metestrus and diestrus. The integrated values (mean ± *SE*) of decreased plasma glucose level from 0 to 6 hr were −14.2 ± 38.2% hr for proestrus, 142.1 ± 94.2% hr for estrus, 364.2 ± 12.7% hr for metestrus, and 378.8 ± 9.3% hr for diestrus.

Vaginal absorption of phenolsulfonphthalein during the estrous cycle is shown by the urinary excretion in Fig. 2. The percentage excreted

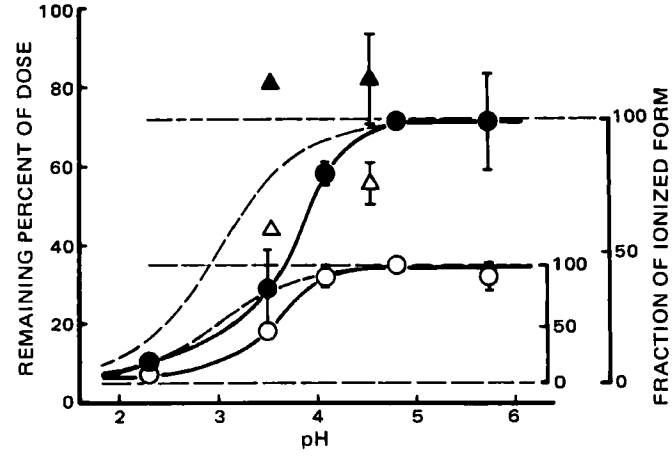

Figure 3—*Remaining percentage of salicylic acid 1 hr after vaginal administration in various pH solutions to diestrous and proestrous rats and fraction of ionized form of the acid. Salicylic acid was administered at a dose of 2 mg/kg/0.2 ml in the buffer solutions, except at pH 2.29 (0.8 mg/kg/0.2 ml). Key: (○) diestrus; [(△) in glycine buffer]; (●) proestrus [(▲) in glycine buffer]; (- -) fraction of the ionized form.*

[3] Polytron, Typ. PT10/35, Kinematica GmbH, Luzern, Switzerland.

Table II—Change in Estrous Cycle of Rats during 10 Daily Subcutaneous Injections of Leuprolide [a]

Rat No.	Day 1	2	3	4	5	6	7	8	9	10	11
1	I	III	IV	V	—[b]	V	V	V	V	V	V
2	I	III	IV	V	—	V	V	V	V	V	V
3	I	III	IV	V	—	V	V	V	V	V	V
4	III	IV	V	V	—	V	V	V	V	V	V
5	III	IV	V	V	—	V	V	V	V	V	V
6	III	IV	V	V	—	V	V	V	V	V	V
7	IV	V	V	V	—	V	V	V	V	V	V
8	IV	V	V	V	—	V	V	V	V	V	V
9	IV	V	V	V	—	V	V	V	V	V	V
10	V	I	III	IV	—	V	V	V	V	V	V
11	V	I	III	IV	—	V	V	V	V	V	V
12	V	I	III	IV	—	V	V	V	V	V	V

[a] (I) proestrus; (III) estrus; (IV) metestrus; (V) diestrus. The analogue was administered once a day at a dose of 100 μg/kg, and the stage of estrous cycle was determined by an examination of vaginal smears each morning. [b] (—) not determined.

(mean ± *SE*) of dose in 6 hr after vaginal administration of phenolsulfonphthalein was 31.4 ± 5.3% during diestrus, 37.5 ± 1.6% during metestrus, 5.5 ± 1.1% during estrus, and 2.4 ± 0.3% during proestrus.

The estrous cycle stage affects vaginal absorption of both insulin and phenolsulfonphthalein.

Vaginal Absorption of Salicylic Acid at Various pHs in Diestrous and Proestrous Rats—The remaining percentage of salicylic acid 1 hr after vaginal administration at various pHs to diestrous and proestrous rats (Table I) are plotted together with the calculated fraction of the ionized form (pK_a of the acid, 3.00) against the pH of the solution in Fig. 3. The disappearance of the acid from the vaginal tract during diestrus was relatively rapid even at pHs where most of the acid was ionized (pH 4.08, 4.80, and 5.73), and the disappearance rate increased at lower pH (pH 3.49 and 2.29). During proestrus the disappearance rate was reduced in nonionized form, but at lower pHs it approached the rate observed during diestrus. The disappearance rate of the ionized form was 66%/hr for diestrus and 29%/hr for proestrus. The absorption from the glycine buffer solutions (pH 3.53 and 4.53) was reduced during both stages.

Vaginal Absorption of Phenolsulfonphthalein after Consecutive Subcutaneous Injection of Leuprolide—After one normal estrous cycle, all rats treated with leuprolide settled in the diestrous stage (Table II). No matter at which stage of the estrous cycle the pretreatment began, the urinary excretion of phenolsulfonphthalein was enhanced ~20% with less variance compared to excretion in the untreated diestrous rats, especially during the 3 hr immediately following vaginal administration (Fig. 4).

DISCUSSION

Vaginal absorption of insulin and phenolsulfonphthalein in rats was dependent on the stage of estrous cycle: absorption was poor during proestrus, slightly improved during estrus, and good during metestrus and diestrus. These results can be explained by changes in vaginal epithelium (3) as follows. The epithelium during metestrus and diestrus is thin and highly porous, so many leukocytes can migrate through it. During proestrus, the superficial layers consist of tightly bound fresh cells and the epithelium is at its thickest. During estrus, the superficial layers become squamous, cornified, and are exfoliated into the vaginal lumen.

To estimate the absorption pathway of hydrophilic and hydrophobic compounds, vaginal absorption for the nonionized and ionized form of salicylic acid was also investigated during proestrus and diestrus. The disappearance of the nonionized acid from the vagina was increased markedly, and similar rates occurred during both stages. The disappearance of the ionized form was different: 66% of the dose in 1 hr during diestrus and 29% during proestrus. In a previous study (1), it was postulated that transport through pore-like pathways, such as intercellular channels, rather than permeation by partition to the cell membrane should cause good absorption of hydrophilic compounds. Thus, the postulation may be supported by the fact that the vaginal absorption of hydrophilic compounds highly depend on the estrous cycle stages which dominate the change of porosity of the membrane. The results also reveal the possibility of vaginal application of hydrophilic compounds during diestrus and metestrus. The high disappearance rate at lowered pHs during both stages possibly are caused by the increased permeation of the nonionized form through the cell membrane, and, in the case of salicylic acid, by the enhancing effect on the mucosal absorption of the drug (7). Since such an enhancing effect was not observed with phenolsulfonphthalein, the vaginal absorption would be more dependent on transport through pore-like pathways. Thus, the apparent porosity during diestrus is presumed to be more than 10 times that during proestrus and estrus (Fig. 2).

In addition, the correlation curve of the remaining percent of salicylic acid with pH during diestrus and proestrus shifted in the direction of higher pH than the theoretical ionized fraction *versus* pH curve (Fig. 3). This phenomenon may be ascribed to the pH difference between bulk solution and the unstirred layer on the membrane or the absorption-enhancing effect of the acid itself. The absorption from glycine buffer was significantly reduced during both proestrus and diestrus. Glycine also reduced the ovulation-inducing activity of leuprolide applied vaginally in an oleaginous base (1). The effects may be due to the stabilizing activity of glycine on the epithelial membrane.

The vaginal epithelium of a mature woman is known to change during the menstrual cycle, and changes of surface ultrastructure have been reported (4). In the follicular phase, the surface of the epithelium consists of a cluster of proliferated, nonkeratinized squamous cells. In the luteal phase, desquamation takes place on the superficial epithelial layer, proceeded by loosening of the intercellular grooves. After ovulation, intercellular porosity is confirmed by the observation of pore-like intercellular crevices and open intercellular connections (dissociated desmosomes). Thus, a similar effect of the reproductive cycle on the vaginal absorption may be expected as observed in rats. The vaginal epithelium is also subject to change with aging (neonate, prepuberty, adult, and senescence), pregnancy, and hormonal disorder. These specific structural changes of vaginal epithelium would influence vaginal absorption, and must be taken into account as a significant factor in the vaginal application of drugs, especially of hydrophilic compounds.

Previously, the continuous administration of leuprolide was found to affect the estrous cycle of rats (5). In the present study, it was confirmed by daily cytological examination of vaginal smears that the cycle was halted at the subsequent diestrus by consecutive treatment with the analogue. During the treatment, the vaginal mucosa was thin and similar to that of normal diestrus except that the smear contained more mucilage.

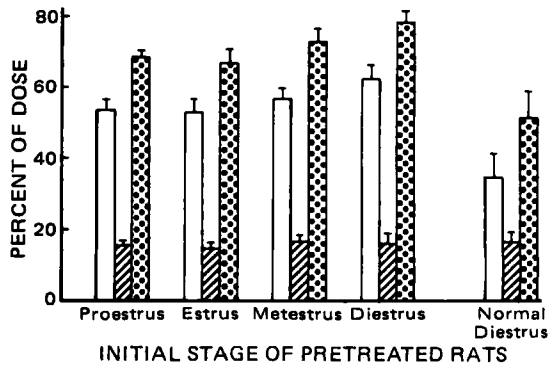

Figure 4—*Urinary excretion of phenolsulfonphthalein after vaginal administration to rats pretreated subcutaneously with leuprolide for 10 days. Phenolsulfonphthalein was administered vaginally at a dose of 2 mg/kg/0.2 ml in 5% citric acid solution (pH 3.5) to rats pretreated with 100 μg/kg/day of the analogue. Each bar represents the mean ± SE of four or five (normal) rats. Key: (□) 0–3 hr; (▨) 3–6 hr; (▩) total.*

Furthermore, the vaginal absorption of phenolsulfonphthalein after the consecutive administration resulted in an enhanced absorption with less variance, regardless of the initial stage of the estrous cycle (Fig. 4). The better absorption supports the halt of the cycle at diestrus and possibly reveals the thinner epithelial membrane.

In long-term therapy with vaginal application of leuprolide, the reproductive cycle effects would be leveled off by continuous administration, either parenterally or vaginally, although some fluctuation in absorption may be unavoidable at the initial period of administration. The authors' previous proposal of the vaginal application of leuprolide as a rational method for long-term anticancer therapy was supported by the findings of the present study.

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Methaqualone–Diphenhydramine Interaction Study in Humans

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Received November 3, 1981, from the **College of Pharmacy and* ‡*College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0.* Accepted for publication April 12, 1982.

Abstract □ Twelve healthy subjects received three single oral doses (250 mg) of methaqualone alone or in combination with diphenhydramine (25 mg). Blood samples were collected for a 48-hr period after each dose and analyzed for methaqualone and its major metabolite, 2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone. Peak blood concentrations ranging from 1.0 to 2.7 μg/ml occurred ~1–2 hr after the oral dose. The area under the blood level–time curve, peak plasma level, and elimination half-life for methaqualone were not significantly different (three-way ANOVA, $p > 0.05$) when methaqualone was administered alone, in combination with a diphenhydramine elixir or as a commercial product (capsule) containing both methaqualone and diphenhydramine. Statistically significant intersubject differences in the area under the curve were eliminated if the area was corrected for subject differences in elimination. Blood levels of the metabolite reached an average peak of 314 ng/ml (±107) between 4 and 8 hr after the dose and remained elevated for the 48-hr sampling period. The areas under the blood level time curve of the metabolite were not significantly different for the three treatments. Diphenhydramine administered at the dosage level used in therapeutic combination products did not alter the blood levels of methaqualone or its metabolite. In addition, no significant differences in methaqualone availability from the two commercial formulations tested could be detected.

Keyphrases □ Methaqualone—interaction study with diphenhydramine in humans, elimination, metabolism □ Diphenhydramine—interaction study with methaqualone in humans, elimination, metabolism □ Elimination—methaqualone–diphenhydramine interaction study in humans, metabolism □ Metabolism—methaqualone–diphenhydramine interaction study in humans, elimination

Although the therapeutic use of the methaqualone–diphenhydramine combination has declined, abuse continues to flourish (1–3). The reasons for the enhanced CNS effects claimed by drug abusers is not clearly understood.

Metabolism of methaqualone by the 10,000-g supernatant fraction of rat liver homogenates is inhibited *in vitro* by diphenhydramine (4). Concurrent oral administration of methaqualone and diphenhydramine to rats increases the blood and brain levels of methaqualone (3), whereas concurrent intravenous administration has no significant effect (5).

In humans, diphenhydramine has been credited with increasing the sedative-hypnotic effect of methaqualone (6), although the mechanism has not been elucidated. A previous study (7) compared methaqualone plasma concentrations achieved after administration of two commercially available diphenhydramine–methaqualone combination products and three methaqualone products. Differences in plasma levels were noted and attributed to formulation factors. An earlier study (8), comparing plasma levels after single dose administration of commercial products containing methaqualone, methaqualone hydrochloride, and methaqualone plus diphenhydramine, is difficult to interpret since no subject appears to have received more than one formulation. In a subsequent study (9) reduction of buccal absorption was reported when methaqualone powder was administered with diphenhydramine powder, but there was no difference in plasma levels after oral administration of the combination.

The objective of the present study was to compare, in healthy subjects, the concentrations of methaqualone and its major metabolite in blood (2-methyl-3-(2′-hydroxymethylphenyl)-4(3H)-quinazolinone), after administration of methaqualone alone and in combination with diphenhydramine. The possibility of a formulation effect was anticipated by including in the study design administration of diphenhydramine–methaqualone as a commercial combination product and as a mixture of a methaqualone capsule and diphenhydramine elixir.

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