Effect of the Spermicide, Nonoxynol 9, on Vaginal Permeability in Normal and Ovariectomized Rabbits

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INTRODUCTION

Vaginal delivery of local and systemically acting drugs has increased over the past decade presumably reflecting greater attention to women's health care. The vaginal route of drug delivery, which offers significant advantages over the oral route in areas of first-pass metabolism, accessibility, and lower metabolic activity, has disadvantages in being subject to change as a result of variation in hormone levels (1) and both the tissue and the vaginal cavity can be potentially influenced by sexual intercourse. There is a growing body of literature (2) relative to changes in drug disposition in the pre- and post-menopausal female but virtually none relative to potential influences of sexual intercourse and agents that may be used during sexual intercourse.

The purpose of the present work is to report on the influence of nonoxynol 9, the most widely used topical contraceptive, on vaginal drug permeability.

MATERIALS AND METHODS

Materials

An enkephalin derivative [D-ala^2,N-methyl-phe^4,-glycol^5][tyrosyl-3,5-^{3}H] enkephalin {[^{3}H]RX 783006}, Amersham Life Science Inc., Arlington Heights, IL, with a specific activity of 58.0 Ci/mmol was used in the diffusion studies. The stability of the tritium label on RX 783006 was tested. Nonoxynol 9 was obtained from Rhone-Poulenc, Cranbury, NJ.

All other materials and solvents were of analytical grade.

Animals and Treatment

Female New Zealand White Rabbits, ex-breeders, weighing 4.5–5 kg (Bakkom's Rabbitry, Viroqua, WI), maintained under a cycle of 12 h light; 12 h darkness with food and water available ad libitum were used throughout the study. The rabbits were ovariectomized under xylazine/ketamine anaesthesia. The animals were allowed to recover for at least four weeks before being used in studies (2). Tissue histology and blood LH levels were used to characterize ovariectomized vaginal tissue (2).

Diffusion Studies

Six side by side diffusion cells (Precision Instrument Design, Los Altos, CA) were used for the diffusion studies. The diffusional area was 0.785 cm^2 and temperature Was maintained at 37°C. pH 7 + 0.3 Sorensen Phosphate buffer was employed in the diffusion experiments. Tonicity of the buffer was adjusted with NaCI (295 mOsm). The solutions were aerated by a gas mixture (O_2/CO_2, 95/5) throughout the study.

After animal sacrifice, vaginal tissue was removed and placed in ice-cold saline solution. Tissue samples were mounted in the diffusion cells with the mucosal surface facing the donor cell. Diffusion experiments were performed for not more than 4 hr. The apparent permeability coefficient (P) of RX 783006 was calculated using the following equation

$$P = [V/AC_0][dC/dt]$$

where V is the volume of the chamber (7 ml), A is the diffusional area of the tissue, C_o is the initial concentration of the donor cell (100%) and dC/dt is the steady state slope of the plot of the percent drug transported vs time.

Statistical analysis of the data was done using student t test.

RESULTS AND DISCUSSION

Commercial topical contraceptive products contain nonoxynol 9 concentration in the range of 2–10%. Because nonoxynol 9 is surface active, solutions containing more than 1% tend to foam and hence in vitro permeability studies were conducted at lower concentrations.

Figure 1 shows the permeability of an enkephalin derivative in intact rabbit vagina in the presence and absence of nonoxynol 9. The permeability effects of 0.42 and 0.83% nonoxynol 9 concentrations are statistically indistinguishable from

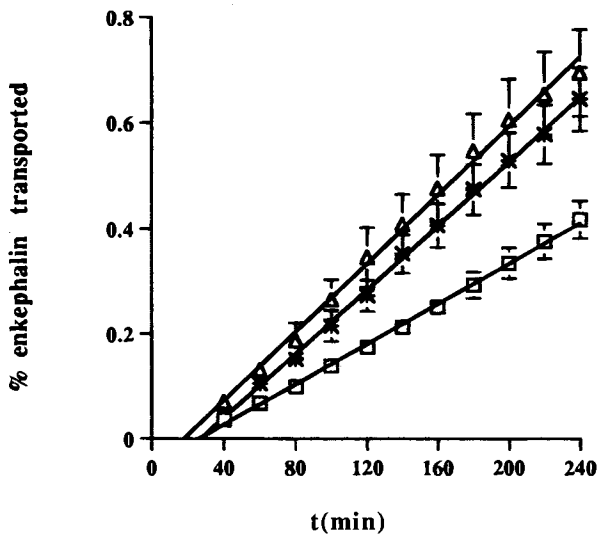

Fig. 1. Effect of nonoxynol 9 concentrations on permeability of RX 783006 in normal rabbit vagina in vitro at pH 7.0. □, control; *, nonoxynol 9 (0.415%); △, nonoxynol 9 (0.83%).

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Table 1. Mean Permeability Coefficients (P) of RX 783006 in the Presence of Nonoxynol 9 in Normal Rabbit Vaginal Mucosa in Vitro at pH 7.0

Rabbit	N[a]	P (cm/sec × 10^{-6})
Control (normal)	23	2.84 (∓0.26)[b]
Nonoxynol 9 (0.415%)	6	4.52 (∓0.20)
Nonoxynol 9 (0.83%)	6	4.83 (∓0.28)

[a] Number of experimental determinations.
[b] Number of parentheses represents the standard error of the mean (SEM).
Note: Differences between RX 783006 permeability measurements (control vs nonoxynol 9) were significant to $p < 0.005$.

each other but both show a statistically significant enhancement over the control. Given that the normal concentrations of nonoxynol 9 used in commercial products is approximately 5–20 times higher than the 0.42% used in this study. It is expected that the effect will be at least as dramatic and probably more so in actual contraceptive use.

Table 1 provides the permeability coefficients in normal rabbit vagina in the presence and absence of nonoxynol 9. Exposure of nonoxynol 9 to the tissue was during the diffusion experiments. Whether or not there is a further increase in permeability upon longer contact time, repeat application, or at higher concentrations is part of a larger ongoing study.

Figure 2 shows the influence of nonoxynol 9 concentration on permeability of the compound across vaginal tissue from an ovariectomized animal.

Earlier studies (2) have shown that the permeability of RX 783006 is significantly enhanced in ovariectomized, relative to normal, rabbit vaginal tissue. The addition of a fairly low level of nonoxynol 9 changes the permeability to this already thin tissue dramatically to the point where linearity cannot be maintained.

In order for the vaginal route to be used as a portal for systemically acting drugs, given the permeability changes that occur as a result of hormone fluctuation and topical contraceptive use, it will be necessary to develop systems where drug availability is controlled by the delivery systems and not absorption across vaginal tissue.

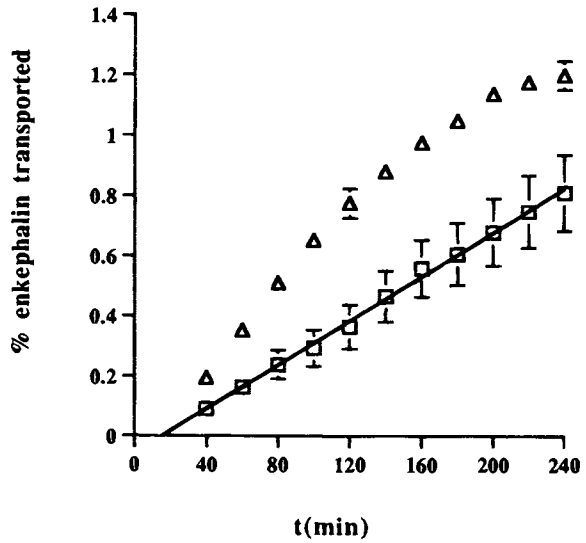

Fig. 2. Effect of nonoxynol 9 on permeability of RX 783006 in ovariectomized rabbit vagina in vitro at pH 7.0. □, ovariectomized control △, nonoxynol 9 (0.83%).

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