Rosamicin in Urethral and Vaginal Secretions and Tissues in Dogs and Rats

UDO HOYME, AXEL BAUMUELLER, AND P. O. MADSEN*

Urology Section, Veterans Administration Hospital, Madison, Wisconsin 53705,* and Department of Surgery, School of Medicine, University of Wisconsin, Madison, Wisconsin 53706

Received for publication 20 April 1977

In animal studies we investigated the distribution of rosamicin in plasma and urethral and vaginal tissues in rats as well as in urethral and vaginal secretions in dogs. We found concentration ratios between urethral secretion and plasma of 1.9 and between vaginal secretion and plasma of 2.4. The rosamicin concentrations in urethral and vaginal tissue significantly exceeded the levels of all other tissues investigated. Because rosamicin could be valuable for the treatment of bacterial urethritis and the colonization of the vaginal introitus with fecal bacteria in women, it should be investigated clinically in this respect.

The mode of secretion by the female paraurethral glands, also called Skene's glands or female prostate, as well as the diffusion across the vaginal epithelium (7) and the cervical excretion (4) seems to have many analogies to the production of prostatic secretion in males (3). The therapy of chronic urethritis or the colonization of the vaginal vestibule with fecal bacteria, preceding urinary tract infections, represents a problem comparable to that of prostatitis.

In animal studies we investigated the distribution of rosamicin (rosamicin sodium dihydrogen phosphate was supplied by Schering Corp., Bloomfield, N.J.) in plasma and urethral or vaginal secretions and tissues. Rosamicin is a new basic macrolide antibiotic with good activity against gram-positive as well as gram-negative bacteria, chlamydia, and mycoplasmas (9).

Previous bacteriological in vitro studies have shown relatively low minimum inhibitory concentrations of rosamicin against a large number of gram-negative microorganisms, even in a moderately acid medium (5), suggesting the possible treatment of nongonococcal urethritis or the colonization of the vaginal vestibule by the most commonly involved bacteria, such as enterobacteriaceae, especially *Escherichia coli* (1, 8).

MATERIALS AND METHODS

Six adult female dogs weighing between 11.2 and 18.2 kg were anesthetized intravenously with sodium thiopental, and the urethra was ligated at the bladder neck to prevent urine contamination. The vagina was exposed through a speculum, and blank paper disks for bioassay determinations were inserted into the urethra and the vagina with a small thread attached, making them easily retrievable.

After 5 min in situ, they were removed and placed on a streptomycin assay agar to determine their rosamicin concentrations by a disk diffusion method, using *Bacillus subtilis* as the test organism. At the same time, blood samples were drawn for bioassay determinations. Pilocarpin, 4 mg, was given intravenously immediately before the antibiotic administration to stimulate the vaginal and urethral secretions. An intravenous bolus of rosamicin (10 mg/kg of body weight) was administered followed by a continuous infusion of 3 mg/kg per h for 4 h. Blood samples were drawn, and the disks were applied immediately after the bolus injection and after 30, 60, 120, 180, and 240 min.

To determine the rosamicin tissue concentrations of the urethra and the vagina in rats, we used 18 albino Sprague Dawley and 18 ACI RC Irish strain, retired breeders, brown female rats, weighing between 160 and 200 g. Additionally, for a comparison with the prostate, 18 male rats of each strain were investigated. The rats were anesthetized by ether inhalation, and the urethra was ligated at the bladder neck. After the injection of rosamicin (20 mg/kg of body weight), six rats in each group were sacrificed at 30, 60, 120, 180, and 240 min after injection. The tissue specimens were removed and homogenized, and their drug concentration was determined by bioassay as previously described.

After the experiments the urethras of the dogs and rats were histologically examined (hematoxylin and eosin stain).

RESULTS

The ratios for rosamicin between vaginal and urethral secretions respectively, and plasma were high in all dogs, highest at the beginning of the test period, and decreasing to fairly constant levels during the last 180 min, with a mean ratio of 1.92 ± 0.21 standard error (SE) for the urethra and 2.38 ± 0.20 SE for the vagina. The results are listed in Table 1.

TABLE 1. *Rosamicin concentrations in plasma and plasma ratios of urethral and vaginal secretions in six female dogs during constant intravenous infusion (mean $\pm$ 1 SE)*

Time (min)	Plasma concn (μ g/ml)	Ratio of urethral secretion/plasma	Ratio of vaginal secretion/plasma
0 ^a	0		
0 ^b	1.73 $\pm$ 0.27	3.96 $\pm$ 0.60	6.78 $\pm$ 2.59
30	0.88 $\pm$ 0.20	3.28 $\pm$ 0.49	3.63 $\pm$ 0.68
60	0.70 $\pm$ 0.08	1.88 $\pm$ 0.13	2.35 $\pm$ 0.18
120	0.48 $\pm$ 0.04	2.55 $\pm$ 0.73	2.67 $\pm$ 0.55
180	0.54 $\pm$ 0.05	1.80 $\pm$ 0.38	2.37 $\pm$ 0.50
240	0.54 $\pm$ 0.14	1.46 $\pm$ 0.16	2.13 $\pm$ 0.40

^a Before bolus.^b Immediately after bolus.

The rosamicin tissue concentrations for albino and ACI brown rats were evaluated together since we could not establish any significant difference between them, despite reports in the literature that there may be such differences (6). The concentrations in urethra and vagina were significantly higher than in the other tissues investigated, e.g., uterus, ovaries, and male urethra as well as ventral, lateral, and dorsal prostatic lobes in rats (Table 2). However, the bladder tissue concentrations were found to be higher, probably due to urine contamination of the mucosa. In these experiments it was remarkable that the plasma level of rosamicin after bolus injection decreased to unmeasurable values within the first 30 min.

Our histological examination demonstrated the existence of multiple ducts and glands in the paraurethral tissue of dogs, whereas we found only a few paraurethral glands and ducts in rats, but never any structures resembling prostatic lobes, as described for some strains (6).

DISCUSSION

In our experiments we investigated for the first time rosamicin in the urethra and vagina of dogs and rats. The mechanisms concerning the diffusion and concentration of drugs into the vagina in levels exceeding the simultaneous plasma values are described by Stamey and Condry (7) as occurring by nonionic diffusion across the vaginal epithelium. There is a great similarity to the diffusion into prostatic secretion (3).

Rosamicin could possibly be an effective drug in the treatment of bacterial urethritis and the colonization of the vaginal vestibule with fecal bacteria since its ratios between plasma and secretions, as shown in this study in dogs, are comparable to ratios found in human vaginal secretion for trimethoprim (7). This occurs al-

TABLE 2. *Rosamicin concentrations in different tissues in 36 female and 36 male rats after bolus injection (mean $\pm$ 1 SE)*

Time (min)	Rosamicin concn (μ g/g) in:									
	Female rats					Male rats				
	Plasma	Urethra	Vagina	Uterus	Ovary	Bladder	Urethra	Prostate		
0 ^a	0	0	0	0	0	0	0	Ventral lobe	Lateral lobe	Dorsal lobe
30	0.31 $\pm$ 0.04	17.6 $\pm$ 10.3	18.5 $\pm$ 9.1	6.9 $\pm$ 1.9	3.9 $\pm$ 1.0	18.5 $\pm$ 8.5	1.0 $\pm$ 0.8	2.0 $\pm$ 1.2	3.8 $\pm$ 2.9	2.2 $\pm$ 0.6
60	0.09 $\pm$ 0.02	10.3 $\pm$ 2.8	25.6 $\pm$ 5.9	7.4 $\pm$ 2.6	2.9 $\pm$ 0.8	33.9 $\pm$ 13.3	5.4 $\pm$ 1.2	4.1 $\pm$ 0.5	3.8 $\pm$ 0.6	3.9 $\pm$ 0.1
120	0.06 $\pm$ 0.01	15.7 $\pm$ 7.4	15.4 $\pm$ 6.0	6.6 $\pm$ 3.0	2.8 $\pm$ 0.6	19.0 $\pm$ 8.8	7.3 $\pm$ 3.9	5.2 $\pm$ 0.8	8.2 $\pm$ 1.8	7.2 $\pm$ 0.7
180	0.06 $\pm$ 0.01	9.5 $\pm$ 2.9	12.9 $\pm$ 4.3	7.8 $\pm$ 2.7	3.1 $\pm$ 0.8	13.1 $\pm$ 3.4	3.0 $\pm$ 1.1	5.9 $\pm$ 0.8	6.3 $\pm$ 2.2	6.6 $\pm$ 0.4
240	0.03 $\pm$ 0.03	15.3 $\pm$ 6.1	16.9 $\pm$ 5.8	7.2 $\pm$ 3.3	2.5 $\pm$ 1.0	6.8 $\pm$ 3.3	2.1 $\pm$ 1.1	4.1 $\pm$ 1.0	4.9 $\pm$ 1.0	6.2 $\pm$ 0.7
								2.5 $\pm$ 0.7	2.0 $\pm$ 0.2	2.8 $\pm$ 0.4

^a Without bolus injection.

though the vaginal pH of 7 to 8.5 in dogs is considerably higher than that in humans, even higher than in postmenopausal women who often suffer from bacterial colonization. Rosamicin, secreted by the urethral epithelium, could possibly reach the depth of the paraurethral glands and ducts in a concentration sufficient to cure bacterial urethritis. The secretion of rosamicin seems to occur immediately after injection, as the high ratio immediately after the bolus administration indicates.

The tissue distribution of rosamicin occurs more rapidly in rats than in dogs, decreasing the drug level in plasma to almost unmeasurable values within the first 30 min. There could be a different mechanism in rats as compared with dogs. It is remarkable that the tissue concentrations of rosamicin in the urethra and vagina were higher than in other tissues. There is an inherent antibacterial activity in prostatic tissue (2), which in our rat experiments even exceeds the rosamicin plasma activity later obtained, but decreasing at the end of the experiment.

Because of its antibacterial spectrum and good distribution in urethral and vaginal secretion and tissue and despite its diminished antibacterial activity at an acid pH, rosamicin may be an alternative drug to presently used antimicrobial agents, e.g., trimethoprim-sulfamethoxazole, in the therapy of urethritis and vagi-

nal colonization. It should be clinically investigated in this respect.

ACKNOWLEDGMENTS

This work was supported by the Medical Research Service of the Veterans Administration.

LITERATURE CITED

1. Elkins, I. B., and C. E. Cox. 1974. Perineal, vaginal and urethral bacteriology of young women. I. Incidence of gram-negative colonization. *J. Urol.* 111:88-92.
2. Fair, W. R., J. Couch, and N. Wehner. 1976. The prostatic antibacterial factor: identity and significance. *Urology* VII:169-177.
3. Madsen, P. O., T. B. Kjaer, A. Baumueller, and H. E. Mellin. 1976. Antimicrobial agents in prostatic fluid and tissue. *Infection* 4(Suppl. 2):154-158.
4. Odeblad, E. 1964. Intracavitary circulation of aqueous material in the human vagina. *Acta Obstet. Gynecol. Scand.* 63:360-368.
5. Schering Corporation. 1976. Information booklet for the investigative drug Sch 14947 (rosamicin). Schering Corp. Bloomfield, N.J.
6. Shehata, R. 1974. Urethral glands in the wall of the female urethra of rats, mice and closely related rodents. *Acta Anat.* 90:381-387.
7. Stamey, T. A., and M. Condry. 1975. The diffusion and concentration of trimethoprim in human vaginal fluid. *J. Infect. Dis.* 131:261-266.
8. Stamey, T. A., M. Timothy, M. Millar, and G. Mihara. 1971. Recurrent urinary infections in adult women. The role of introital enterobacteria. *Calif. Med.* 115:1-19.
9. Wagman, G. H., J. A. Waitz, J. Marquez, A. Murawski, E. M. Oden, R. T. Testa, and M. J. Weinstein. 1972. A new micromonospora-produced macrolide antibiotic, rosamicin. *J. Antibiot.* 25:641-642.