ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1977, p. 240-242

Vol. 12, No. 2
Printed in U.S.A.

Rosamicin—a New Drug for the Treatment of Bacterial Prostatitis

AXEL BAUMUELLER, UDO HOYME, AND PAUL 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

Rosamicin, a new macrolide substance, was investigated in dogs and humans with regard to its usefulness for the treatment of bacterial prostatitis and compared with the well-known macrolide erythromycin. In dogs with normal and experimentally infected prostates, concentration ratios for rosamicin in prostatic secretion, interstitial fluid (obtained from implanted tissue chambers), and tissue were significantly higher than for erythromycin. The difference was even more pronounced in human prostatic tissue, obtained by transurethral resection. With its broad spectrum against many common urinary pathogens, rosamicin seems to be a promising drug for the treatment of acute and chronic bacterial prostatitis.

Rosamicin is a new antibacterial substance, a macrolide resembling erythromycin (1, 4, 6–8). It is a base with a pK_a of 8.7 and minimum water solubility, but good lipid solubility. It is heat and pH stable, and its antibacterial activity is increasing at alkaline pH. The minimum inhibitory concentrations at moderately acid pH (such as in prostatic fluid) are also at relatively low levels for bacteria, commonly causing bacterial prostatitis (4). Rosamicin is well absorbed in active form after oral administration.

The antibacterial spectrum of rosamicin consists of both gram-positive and gram-negative bacteria, but the activity against gram-positive bacteria is greater. Compared with erythromycin, rosamicin is more effective against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella* and *Proteus* species. Due to these features, this compound appears to be of interest in the treatment of bacterial prostatitis, since for any compound to concentrate in prostatic secretion the substance has to be a base with high lipid solubility and a pK_a higher than that of plasma (3, 5).

We, therefore, compared the concentrations of rosamicin in canine prostatic secretion, interstitial fluid, and tissue with the levels of the well-known macrolide erythromycin. In a separate trial, rosamicin and erythromycin were compared in human prostatic tissue and secretion.

MATERIALS AND METHODS

Dog experiments. Nine dogs, weighing between 16 and 23 kg, were anesthetized intravenously with sodium thiopental. Through a paramedian incision, the bladder neck was ligated with a rubber tourniquet, and the urine was diverted temporarily by a suprapubic cystostomy. A vasectomy was performed and prostatic secretion was obtained via the catheterized urethra for bacterial cultures. Thereafter, in each lobe of the prostate, a small tissue chamber was implanted (2, 9).

After 1 month, assuming that the tissue chambers were healed completely in, in four of these dogs an experimental bacterial prostatitis was created by the injection of *E. coli* bacteria into a branch of the prostatic artery. The development of the prostatitis was later confirmed in all dogs in which infection was induced by positive cultures for *E. coli* from prostatic tissue and secretion as well as by histology.

The drug studies were carried out by using a constant infusion technique. After a bolus injection of 10 mg of either rosamicin or erythromycin per kg, a constant intravenous infusion of 3 mg/kg per h was administered. Samples of plasma, prostatic secretion, and prostatic interstitial fluid were obtained before and after administration of the bolus and every 30 min thereafter for 4 h.

To assess the drug levels in prostatic tissue, studies were done in eight additional dogs by constant infusion techniques as mentioned before. At the end of the experiments, the prostate glands were removed and tissue samples were taken for drug determinations (A. Baumueller, T. B. Kjaer, and P. O. Madsen, Invest. Urol., in press).

To compare the individual experiments, the concentration ratios between plasma, prostatic secretion, interstitial fluid, and tissue, respectively, were determined. For the calculation of plasma levels, the averages of the concentrations, as measured at the beginning and at the end of each collecting period, were taken.

Patient studies. Nine patients with benign pros-

tatic hyperplasia undergoing transurethral resection of the prostate gland received 1,000 mg of rosamicin daily (250 mg every 6 h) for 24 h before surgery. The last tablet was given 1 to 2 h before the operation with the patients' premedication for surgery. Another nine patients received 1,000 mg of erythromycin gluceptate orally (250 mg every 6 h) for 24 h before surgery, the last dose also being given 1 to 2 h prior to surgery.

Serum samples were drawn at the beginning, during, and at the conclusion of the transurethral resection of the prostate. The prostatic tissue chips were removed from the bladder immediately after resection to prevent a possible washout of the drugs into the irrigating fluid.

To monitor possible influences on the concentrations in the tissue samples, the antibiotic levels in the irrigating fluid and urine were determined in all patients.

A patient with high urinary diversion for neurogenic bladder received 1,000 mg of rosamicin or erythromycin daily (250 mg every 6 h) in separate trials at 2-month intervals. Serum samples were drawn and prostatic secretion was obtained by prostatic massage at intervals after the last dose. From one patient receiving erythromycin preoperatively prostatic secretion was also obtained by prostatic massage immediately before surgery.

All samples were frozen and stored at −17°C until the bioassay determination, which was carried out within 2 weeks. The concentrations of either drug in prostatic tissue, interstitial fluid, and secretion were determined by using a disk diffusion technique with *Bacillus subtilis* as the test organism for rosamicin and *Sarcina lutea* as the test organism for erythromycin. The prostatic tissue (approximately 0.5 g) was homogenized for a few seconds in 1 ml of normal saline before the bioassay. Standards for bioassays were set up by dilution with pooled canine prostatic secretion for canine prostatic secretion, by dilution with phosphate buffer (pH 8.0) for prostatic interstitial fluid, and by dilution with pooled plasma for plasma.

In those cases in which more than one value for the drug concentration in prostatic tissue, interstitial fluid, secretion, or plasma were obtained, the average was used to calculate the concentration ratios.

RESULTS

Table 1 shows the results of our studies in dogs. Rosamicin is in all cases significantly more concentrated than erythromycin. The differences between the ratios of prostatic tissue to plasma are only of borderline significance. On the other hand, the differences between the more representative ratios of prostatic interstitial fluid to plasma are highly significant. To evaluate the usefulness of the prostatic tissue determinations in patients (from whom interstitial fluid cannot be obtained), we compared the canine ratios of tissue to plasma with the ratios of interstitial fluid to plasma obtained at the end of each study. There were no statistical differences between these values ($P < 0.5$ for erythromycin; $P < 0.4$ for rosamicin).

The actual effect of the drugs on the induced prostatitis was not evaluated since the dogs were sacrificed immediately after the experiments to investigate the histological appearance of the prostatitis and the tissue reactions to the implanted chambers.

Table 2 lists the values in the patient trials, comparing the ratios of tissue to plasma of the two antibiotics. The plasma levels of rosamicin were much lower than the erythromycin levels, whereas with the prostatic tissue concentrations the reverse was true. This is reflected in the ratios of tissue to plasma.

The same results seemed to be obtained for the human prostatic secretion (Table 3).

DISCUSSION

The objective of our studies was to investigate the potential value of rosamicin for the antimicrobial treatment of bacterial prostatitis. As we showed in the dog experiments, the rosamicin concentration ratios for prostatic secretion, interstitial fluid, and tissue were all higher than the corresponding erythromycin ratios. It is especially interesting that the drug

TABLE 1. *Concentration ratios for rosamicin and erythromycin in prostatic secretion and interstitial fluid, respectively, to plasma in nine dogs with normal (n = 5) and infected prostate glands (n = 4) and prostatic tissue values from four additional dogs with normal prostates*

Prostatic secretion/plasma ratio (n = 9)		Prostatic interstitial fluid/plasma ratio (n = 9)		Prostatic tissue/plasma ratio (n = 4)	
Rosamicin	Erythromycin	Rosamicin	Erythromycin	Rosamicin	Erythromycin
8.9 ± 2.7[a]	4.0 ± 1.8	4.0 ± 1.5	2.4 ± 1.1	3.4 ± 1.2	1.7 ± 1.0
4.5–16[b]	1.0–9.1	1.5–9.0	0.8–6.2	1.8–4.5	1.0–3.2
$P < 0.001$[c]		$P < 0.001$[c]		$P < 0.1$[c]	

[a] Mean ± 1 standard deviation.
[b] Range.
[c] Determined by the Student t test.

TABLE 2. *Rosamicin and erythromycin concentrations in serum and prostatic tissue and the ratios of prostatic tissue to serum*

Drug	No. of patients	Concn (μg/ml)		Ratio of prostatic tissue to serum
		Serum	Prostatic tissue	
Rosamicin	9	0.07[a]	2.4	31.8
		0.06–0.14[b]	0.5–3.8	3.8–69.1
Erythromycin	9	0.42	0.58	0.9
		0.23–1.16	0.14–1.05	0.6–1.5

[a] Median.
[b] Range.

TABLE 3. *Erythromycin and rosamicin concentrations in human serum and prostatic secretion in two patients*

Time after last dose (h)	Drug concn (μg/ml) in:								
	Patient SH						Patient SC (erythromycin)		
	Erythromycin			Rosamicin					
	Serum	Prostatic secretion	Ratio of prostatic secretion to serum	Serum	Prostatic secretion	Ratio of prostatic secretion to serum	Serum	Prostatic secretion	Ratio of prostatic secretion to serum
1	0.38	0.34	0.9	0.09	10	111			
2	0.37			0.08			0.53	0.2	0.37
3	0.27	0.41	1.5	0.09	19	211			

concentrations at the site of potential inflammatory processes in the interstitial tissue were significantly higher than the plasma levels. Since it is impossible to measure prostatic interstitial fluid levels in humans, it is important to notice that in our dog experiments no statistical difference between the ratios of interstitial fluid to plasma and tissue to plasma could be demonstrated. We, therefore, assume that our ratios of human prostatic tissue to plasma reflected the drug concentrations at the site of an inflammation. These ratios were very high for rosamicin, and it is not surprising that the ratios for human prostatic secretion were even higher, but due to the small number of patients no definite conclusion can be drawn from this.

When the ratios of tissue to plasma from dogs and patients are compared, it is remarkable that although there exists no difference for erythromycin between the two species, the ratios for rosamicin obtained in humans were 10 times higher than those obtained in dogs.

We conclude that rosamicin is highly concentrated in the prostate gland of humans as well as dogs. Since the antimicrobial spectrum of this new macrolide is very promising with regard to many common urinary pathogens, rosamicin may be of value in the antimicrobial treatment of acute and chronic bacterial prostatitis and should be tested in clinical trials.

ACKNOWLEDGMENT

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

LITERATURE CITED

1. Crowe, C. C., and W. E. Sanders, Jr. 1974. Rosamicin: evaluation in vitro and comparison with erythromycin and lincomycin. Antimicrob. Agents Chemother. 5:272–275.
2. Eickenberg, H.-U., N. G. Waterman, and L. Scharfenberger. 1975. Concentrations of antibiotics in renal interstitial fluid: an experimental model. Urol. Res. 3:165–167.
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. Schering Corporation. 1976. Information booklet for the investigative drug Sch 14947 (rosamicin). Schering Corp., Bloomfield, N.J.
5. Stamey, T. A. 1972. Urinary infections, p. 191–199. The Williams and Wilkins Co., Baltimore.
6. Sutter, V. L., and S. M. Finegold. 1976. Rosamicin: in vitro activity against anaerobes and comparison with erythromycin. Antimicrob. Agents Chemother. 9:350–351.
7. 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.
8. Waitz, J. A., C. G. Drube, E. L. Moss, Jr., and M. J. Weinstein. 1972. Biological studies with rosamicin, a new micromonospora-produced macrolide antibiotic. J. Antibiot. 25:647–652.
9. Waterman, N. G., and L. B. Kastan. 1972. Interstitial fluid and serum antibiotic concentrations. Arch. Surg. (Chicago) 105:192–196.