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Comparative Pharmacology of Josamycin and Erythromycin Stearate

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Two macrolide antibiotics, josamycin and erythromycin stearate, were administered orally to healthy, adult male volunteers for a comparative study of their pharmacological properties. In comparable doses, josamycin and erythromycin produced similar plasma concentrations, with similar half-lives and elimination constants. An initial loading dose of 1.5 g of josamycin produced greater peak concentrations of antibiotic throughout a 10-day period with a regimen of every 6 h. In addition, josamycin tended to reach higher peak and trough concentrations after regimens of every 6 or 8 h were maintained for 2 days. Josamycin penetrated into saliva, sweat, and tears, and it was better tolerated in fasting subjects than was erythromycin stearate.

Josamycin is a macrolide antibiotic produced by *Streptomyces narbonensis* subsp. *josamyceticus*. Its spectrum of bacteriostatic activity is similar to that of erythromycin. Concentrations of 0.5 μg/ml inhibit most strains of *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, and *S. pyogenes* in vitro (6, 7). *Corynebacterium diphtheriae*, *Neisseria meningitidis*, *N. gonorrheae*, and *Bordetella pertussis* appear to be equally susceptible (6). A number of anaerobic bacteria, including *Bacteroides fragilis*, are susceptible to concentrations of 2 μg/ml (6, 7). Most strains of *Staphylococcus aureus* are also susceptible to concentrations of 2 μg/ml (6, 7). Josamycin inhibits most erythromycin-resistant staphylococci and, unlike erythromycin, it does not induce macrolide resistance in these strains (6).

Clinical trials with josamycin were initiated by Japanese investigators in 1967. The results of therapy in 785 patients with various infections have been reported (6). Josamycin was considered to be effective therapy in 82% of these patients, and on clinical grounds it was judged to have the same efficacy as erythromycin. Josamycin therapy was not associated with hematological, renal, hepatic, or other definable toxicity. Side effects were infrequent. Mild gastrointestinal disturbances such as anorexia and epigastric distress or nausea were noted by 4% of the treated patients, but discontinuation of josamycin was seldom required.

In spite of these favorable reports from Japan, the position of josamycin among the macrolide antibiotics has not been established, nor have the advantages that josamycin may offer over erythromycin been identified. The present study was designed to: (i) compare the pharmacokinetics, toxicity, and tolerance of orally administered josamycin and erythromycin stearate in 21 healthy, young male adults during a 4-day multidose cross-over trial; (ii) examine serum concentrations, toxicity, and tolerance in four subjects during a 10-day course of josamycin preceded by a loading dose, and (iii) determine the penetration of josamycin into urine, saliva, sweat, and tears.

MATERIALS AND METHODS

Antibiotics. Josamycin and erythromycin stearate were supplied by Endo Laboratories Inc., Garden City, N.Y.

Human volunteers. Twenty-one healthy men aged 23 to 35 years volunteered to participate in this study. Informed written consent was obtained. Their weights ranged from 71.8 to 89.1 kg. All subjects had normal creatinine clearances. None of the volunteers were taking any other antimicrobial agents during the investigational period.

Procedure. In the first part of this study, 21 subjects were randomly divided into groups of seven. Each group was then assigned to a different sequence of three antibiotic regimens to be taken during three dosing periods. Each period was 4 days in length, and there were 10 days between each period. During each of the three periods, one group was receiving 500 mg of josamycin orally every 8 h, one group was receiving 500 mg of josamycin orally every 6 h, and one group was receiving 500 mg of erythromycin orally every 6 h or 250 mg orally every 6 h. Because adverse gastrointestinal side effects during the first dosing period prompted two of seven subjects receiving 500 mg of erythromycin orally every 6 h to discontinue therapy, the dosage was

decreased for the other two groups during the subsequent periods. One subject failed to conform to the dosage time schedule while on 500 mg of josamycin every 6 h and, therefore, his plasma concentrations were not included in the final analysis. Compliance was otherwise good. One subject inadvertently omitted one dose of josamycin during both the 6-h and 8-h schedules, and two subjects missed the final 1.5 days of the 250-mg erythromycin trial.

All subjects fasted for 12 h before each dosing period. A control venous blood sample was drawn prior to the first dose; no antibiotic activity was detectable in the 0-h bloods of any subject during the three dosing periods. After the first dose, all subjects fasted for 2 h before and after each subsequent dose. Venous blood samples for assay of plasma antibiotic concentration were obtained at 0.5, 1, 2, 3, 4.5, 6, 8, 12, 24, 48, 48.5, 49, 50, 51, 52.5, 54, 55, 56, 57, 58.5, 60, 72, 84, and 96 h. Plasma samples were frozen to −70°C. Antibiotic assays were performed (within 2 weeks). This method of storage did not affect the drug concentrations in the samples.

The following tests for possible adverse effects were performed twice before and once after each dosing period: hemoglobin, hematocrit, leukocyte count and differential, platelet estimation, urinalysis, serum glutamic oxaloacetic acid transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, total bilirubin, lactate dehydrogenase, blood urea nitrogen, fasting glucose, sodium, potassium, chloride, CO_2 combining power total protein, albumin, cholesterol, triglycerides, thyroxine, and electrocardiogram. In addition, the blood pressure and pulse were checked twice daily during each dosing period. All subjects were questioned daily during therapy.

In the second phase of this study four subjects received a 1,500-mg loading dose and then 500 mg orally every 6 h to complete a 10-day course. Subjects fasted 2 h before and 2 h after each dose. One subject withdrew from the study on day 9 because of gastrointestinal symptoms. Plasma samples were collected, at 0.33, 0.5, 0.67, 1, 2, 3, 4.5, 6, 8, 12, 24, 24.5, 25, 26, 30, 30.5, 31, 32, 54, 72, 72.5, 73, 74, 78, 78.5, 79, 80, 96, 168, 168.5, 170, 174, 174.5, 175, 176, 192, 198, 216, 216.5, 217, 218, 222, 222.5, 223, 224, and 240 h. A 24-h urine was collected between 0 and 24 h and between 168 and 192 h for determination of the josamycin concentration. Ten samples of saliva, seven samples of sweat, and six samples of tears were obtained at random from the four subjects during the 10 days of therapy for determination of josamycin concentration. Saliva was expectorated into sterile cups; in some cases salivation was stimulated by the chewing of paraffin. Sweat was collected with an ionphoresis analyzer. Tearing was induced with chemical and mechanical stimuli, and tears were then collected with a sterile tuberculin syringe. These four subjects were monitored for toxicity and side effects as in the previous study.

Antibiotic assays. The concentrations of josamycin or erythromycin were determined by an agar well diffusion technique, using *Sarcina lutea* ATCC 9341 as the test organism and antibiotic medium no. 11 (Difco). Reference standards were diluted in pooled human plasma for plasma assays, potassium phosphate buffer (pH 8) for urine assays, human saliva for saliva assays, and normal saline for sweat and tear assays. Urine samples were diluted in potassium phosphate buffer and adjusted to pH 8. All samples and standards were tested in triplicate. Assay plates were incubated at 37°C for 18 h. Zones of inhibition were measured with a Fisher Lilly zone reader. Antibiotic concentrations were computed by comparing the mean zone of inhibition for each sample with the curve constructed from the zone sizes of the standard dilutions.

Calculation of plasma half-life. Mean plasma concentrations obtained between 0 to 8 h and 48 to 56 h were plotted on semilog graph paper versus time. The half-life ($t_{1/2}$) was determined from the best-fit line through the points during the decline of blood levels, using the method of least squares.

The elimination rate constant (Kd) was determined from the formula: $Kd = 0.693/t_{1/2}$.

RESULTS

Josamycin and erythromycin stearate pharmacokinetics. The plasma concentration of josamycin usually peaked within 1 h after dosing and declined steadily over the next 5 h (Tables 1 and 2). At 1 h after the first 500-mg tablet, plasma concentrations for the two josamycin groups ranged between 0 and 1.43 μg/ml, with means of 0.71 and 0.61 μg/ml. After 6 h josamycin was not detectable in the plasma of most subjects. Higher plasma concentrations were observed on day 3. At 49 h the plasma concentrations in the 8-h group varied between 0 and 4.69 μg/ml, with a mean of 1.64 μg/ml, and in the 6-h group the concentrations ranged between 0.18 and 6.66 μg/ml, with a mean value of 2.31 μg/ml. The trough concentrations also increased during the first 2 days of therapy. At 48 h the mean concentration was 0.09 μg/ml in the 8-h group and 0.34 μg/ml in the 6-h group. This gradual increase in trough plasma concentrations leveled off after 54 h. With the 6-h schedule mean plasma concentrations were 0.45 μg/ml at 60 h, 0.46 μg/ml at 72 h, 0.40 μg/ml at 84 h, and 0.48 μg/ml at 96 h.

Plasma concentrations of erythromycin stearate were maximal between 1 and 3 h after each dose (Tables 3 and 4). At 2 h the 250-mg group had concentrations between 0 and 5.49 μg/ml, with a mean of 0.76 μg/ml. At 3 h the 500-mg group demonstrated plasma concentrations between 0.72 and 1.70 μg/ml, with a mean of 1.18 μg/ml. After 6 h the mean concentration was 0.14 μg/ml in the 250-mg group and 0.30 μg/ml in the 500-mg group. Plasma concentrations of erythromycin also increased slightly over the first 2 days. At 50 h the mean plasma concentration varied between 0 and 5.0 μg/ml, with a mean of 1.50 μg/ml in the 250-mg group,

TABLE 1. *Josamycin plasma concentrations in 21 subjects (500 mg every 8 h)*

Subject no.	Plasma concn (μg/ml) on day 1 at h:					Plasma concn (μg/ml) on day 3 at h:								
	0.5	1	2	3	4.5	48	48.5	49	50	51	52.5	54	55	56
1	0.73	0.92	0.53	0.34	0	0	0.34	0.82	0.60	0.31	0.23	0	0	0
2	1.32	0.56	0.35	0	0	0	0.79	1.11	0.78	0.47	0.28	0.24	0	0
3	0	1.43	0.46	0.38	0	0.17	0.76	2.90	0.73	0.96	0.53	0.46	0.35	0.30
4	0.83	0.87	0.36	0.30	0	0	0	0	0.35	0.42	0.25	0	0	0
5	0.58	0.98	0.45	0.51	0	0	0.40	1.42	1.06	0.45	0.25	0	0	0
6	0	0	0.28	0.27	NS[a]	0.30	0.44	1.50	1.25	1.17	0.53	0.54	0.46	0.35
7	0.28	0.79	0.31	0	0	0	1.67	1.25	0.52	0.22	0	0	NS	0
8	0	0.78	0.64	0.24	0.14	0.20	0.31	2.51	1.49	1.53	0.60	0.62	0.50	0.43
9	0.46	0.64	0.45	0.46	0	0.42	1.08	2.97	3.59	0.80	0.48	0.38	0.28	0.29
10	NS	1.10	0.36	0.33	0	0.37	4.75	3.18	2.26	0.67	0.45	0.32	0.28	0.28
11	0.65	0.36	0.29	0.36	0	0	1.58	4.69	0.76	0.61	0.34	0.24	0	0
12	0	0.53	0.36	0.26	0	0	0	1.54	0.93	0.68	0.35	0.32	0.27	0
13	1.38	0.53	0.35	0.27	0	0	0.37	0.40	0.32	0.29	0.23	0	0	0
14	0.56	0.73	0.36	0.25	0	0	0	0	0	0	0	0	0	0
15	0.21	0.22	0.25	0.27	0	0	0	1.79	0.90	0.58	0.30	0.25	0	0
16	0.67	0.40	0.31	0	0	0	0.39	2.79	2.18	0.82	0.48	0.32	0.28	0.27
17	0.61	0.95	0.56	0.52	0.18	0.31	1.69	2.32	1.40	1.45	0.67	0.65	0.55	0.41
18	0	0.26	0.23	0	0	0	0	0.39	1.24	0.44	0.38	0.20	0	0
19	1.79	0.84	0.39	0.26	0	0	0.60	1.51	0.79	0.45	0.23	0	0	0
20	0.28	0.62	0.28	0.25	0	0	0.79	0.96	0.52	0.48	0.24	0	0	0
21	1.47	1.38	0.56	0.37	0.25	NS	0.50	0.35	0.35	0.17	0	0	NS	0
Mean	0.59	0.71	0.39	0.27	0.03	0.09	0.78	1.64	1.04	0.62	0.32	0.22	0.16	0.11

[a] NS, No sample.

TABLE 2. *Josamycin plasma concentrations in 20 subjects (500 mg every 6 h)*

Subject no.	Plasma concn (μg/ml) on day 1 at h:						Plasma concn (μg/ml) on day 3 at h:						
	0.5	1	2	3	4.5	6	48	48.5	49	50	51	52.5	54
1	0	1.23	0.48	0.33	0	0	0.15	1.76	2.18	0.73	0.69	0.26	0.21
2	0.79	0.53	0.31	0	0	0	0.39	1.54	2.28	2.07	0.64	0.44	0.36
3	0	1.20	0.54	0.32	0.28	0	0.41	0.55	1.76	1.43	1.06	0.78	0.51
4	0.72	0.26	0.25	0.28	0	0	0.58	0.76	1.14	0.80	0.97	0.51	0.41
5	0.63	0.38	0.27	0	0	0	0	1.39	0.56	0.31	0.14	0	0
6	0	0.82	0.75	0.44	0.41	0	0.79	0.76	3.19	2.50	1.62	0.98	1.28
7	0	0	0	0	0	0	0	1.36	1.40	1.04	0.35	0.25	0
8	1.41	0.76	0.48	0.36	0	0	0.50	0.55	3.05	4.58	1.06	0.94	0.46
9	0.23	0.41	0.45	0.19	0	0	0.37	1.05	2.68	1.57	1.16	0.71	0.50
11	0.60	0.34	0.29	0.18	0	0	0.27	0.37	1.57	0.98	0.85	0.81	0.42
12	0	0.68	0.38	0	0	0	0.46	0.93	5.73	2.50	1.03	0.53	0.41
13	0.35	0.22	0	0	0	0	0.24	0.35	0.45	0.41	0.27	0	0.98
14	1.50	0.58	0.31	0.31	0	0	0	0	0.18	0.80	0.47	0.29	0.33
15	0.64	0.39	0.34	0.31	0	0	0.35	0.27	2.72	1.47	0.47	0.32	0.26
16	0.32	0.43	0.40	0.25	0	NS[a]	0.48	1.84	1.73	1.50	1.09	0.95	0.46
17	1.27	1.12	0.69	0.56	0.33	0.17	0.71	1.43	3.30	2.72	1.36	1.04	1.02
18	0.95	0.46	0.29	0.40	0	0	0	3.84	2.34	0.51	0.42	0	0
19	0.66	0.20	0.44	0.31	0	0	0.22	0.27	1.68	1.43	0.95	0.47	0.40
20	0	1.21	0.36	0.35	0	0	0	0.32	1.52	1.93	0.66	0.37	0.37
21	0.31	1.00	0.74	0.47	0.41	0	0.90	1.48	6.66	5.30	1.02	0.59	0.86
Mean	0.52	0.61	0.39	0.25	0.07	0.01	0.34	1.04	2.31	1.73	0.81	0.51	0.46

[a] NS, No sample.

and at 51 h in the 500-mg group the plasma concentrations were between 0.61 and 3.57 μg/ml, with a mean of 1.44 μg/ml. At 54 h the mean plasma levels had declined to 0.24 μg/ml in the 250-mg group and 0.56 μg/ml in the 500-mg group. Plasma concentrations at 60, 72, 84, and 96 h were comparable to those at 54 h.

The decline in mean plasma concentrations

TABLE 3. *Erythromycin plasma concentrations in 14 subjects (250 mg of erythromycin stearate every 6 h)*

Subject no.	Plasma concn (μg/ml) on day 1 at h:						Plasma concn (μg/ml) on day 3 at h:						
	0.5	1	2	3	4.5	6	48	48.5	49	50	51	52.5	54
1	0	0.68	0.97	NS[a]	0.26	0.05	0.06	0.39	0.55	1.37	0.89	0.15	0.13
2	0	0	0.19	0.13	0.06	0.04	0.05	0	0.26	0.62	0.53	0.23	0.08
5	0	0.10	0	1.76	0.29	0.20	0.03	0.10	0.43	1.82	1.74	0.12	0.06
6	0	0.55	0.20	1.15	0.36	0.26	0.68	0.46	0.66	0.83	1.31	1.37	0.87
7	0	0	1.40	0.48	0.09	0.17	0	0.05	0	4.07	0.32	0.13	0.07
9	0.04	0.10	0.61	0.31	0.18	0.10	0.13	0.11	0.80	1.40	1.27	0.95	0.74
10	0	0.12	5.49	0.65	0.15	0.26	0.03	0.04	0.13	2.37	0.27	0.09	0.07
12	0	0	0	0.22	0.22	0.12	0.20	0.15	0.43	0.46	0.74	0.52	0.43
14	0	0	0.17	0.22	0	0	0.03	0.04	0	0	0.09	0.07	0.04
15	0	0.24	0.05	0.35	0.16	0.10	0.07	0.06	0.44	0.34	0.81	0.40	0.12
16	0.04	0.70	0.45	0.34	0.12	0.08	0.13	0.11	0.16	0.36	1.54	0.67	0.26
18	0	0.13	0.37	0.28	0.17	0.24	0.12	0.12	0.38	1.56	0.40	0.13	0.08
19	0.05	0.13	0.42	0.59	0.33	0.14	0.08	0.07	0.80	0.74	0.64	0.35	0.12
21	0	0.34	0.33	0.71	0.12	0.13	0.83	0.65	2.46	5.00	0.82	0.44	0.28
Mean	0.009	0.22	0.76	0.55	0.18	0.14	0.17	0.17	0.54	1.50	0.81	0.40	0.24

[a] NS, No sample.

TABLE 4. *Erythromycin plasma concentrations in seven subjects (500 mg of erythromycin stearate every 6 h)*

Subject no.	Plasma concn (μg/ml) on day 1 at h:						Plasma concn (μg/ml) on day 3 at h:						
	0.5	1	2	3	4.5	6	48	48.5	49	50	51	52.5	54
3	0.24	1.05	1.93	1.70	1.14	0.74	0.16	0.31	0.99	2.51	0.79	1.03	0.85
4	0	0.38	0.75	1.17	0.30	0.12	1.97	0.76	2.26	2.10	1.74	1.07	0.53
8	0	1.02	0.67	0.92	0.28	0.14	NS[a]	NS	NS	NS	NS	NS	NS
11	0.03	0.14	0.72	0.72	0.21	0.08	0.37	0.47	0.43	0.75	0.61	1.21	0.39
13	0	0.38	0.81	0.98	0.47	0.25	0.26	0.54	0.65	1.13	0.93	1.13	0.44
17	0.22	0.86	1.81	1.14	0.70	0.28	0.73	0.71	1.16	1.15	3.57	1.54	0.87
20	0	0.24	0.94	1.61	0.81	0.48	0.27	0.27	0.40	0.41	0.97	0.59	0.29
Mean	0.07	0.58	1.09	1.18	0.56	0.30	0.63	0.51	0.98	1.34	1.44	1.10	0.56

[a] NS, No sample.

for each dosage group between 0 to 6 or 8 h and 48 to 54 or 56 h was used to determine the plasma half-life (Table 5). The plasma half-life determinations ranged between 1.34 and 1.56 h for josamycin and between 1.42 and 1.89 h for erythromycin. The elimination constant or the fraction of drug eliminated each hour varied between 0.45 and 0.52/h for josamycin and between 0.37 and 0.49/h for erythromycin.

The addition of a 1.5-g loading dose increased the peak and trough plasma concentrations of josamycin (Table 6). Plasma concentrations at 1 h on day 1 of therapy ranged between 3.94 and 6.47 μg/ml, with a mean of 5.06 μg/ml. Although the peak plasma concentrations were not as high on subsequent days, they tended to exceed those obtained in the 6-h josamycin group without a loading dose (mean, 2.31 μg/ml at 1 h on day 3). With the loading dose, the mean plasma concentration at 1 h was 3.18 μg/ml on day 2, 2.73 μg/ml on day 4, 3.62 μg/ml on day 8, and 2.61 μg/ml on day 10. The trough concentrations obtained at 0 and 6 h also tended to be higher after a loading dose. The mean trough plasma concentrations varied between 0.45 and 1.04 μg/ml during the 10 days of ther-

TABLE 5. *Plasma half-life and elimination constant for josamycin and erythromycin*

Drug	Dosage schedule	Observation period (h)	Plasma half-life (h)	Elimination constant/h
Josamycin	500 mg every 8 h	0–8	1.48	0.47
		48–56	1.53	0.45
Josamycin	500 mg every 6 h	0–6	1.56	0.45
		48–54	1.34	0.52
Erythromycin	250 mg every 6 h	0–6	1.55	0.45
		48–56	1.72	0.40
Erythromycin	500 mg every 6 h	0–6	1.42	0.49
		48–54	1.89	0.37

TABLE 6. *Josamycin plasma concentrations during a 10-day trial*[a]

Day of therapy	Subject no.	Plasma concn (μg/ml) at time (h) after first morning dose:				
		0	0.5	1	2	6
1	101	0	NS[b]	6.47	5.23	0.90
	102	0	NS	4.97	4.89	1.26
	103	0	2.25	3.94	3.71	0.65
	104	0	3.64	4.86	1.98	0.43
Mean			2.94	5.06	3.95	0.81
2	101	0.45	0.88	3.53	1.73	0.51
	102	0.72	1.52	4.25	2.65	1.06
	103	0.52	0.76	3.35	2.71	0.80
	104	0.10	1.81	1.58	0.68	0.21
Mean		0.45	1.24	3.18	1.94	0.64
4	101	1.23	NS	3.22	2.53	1.26
	102	1.47	NS	3.46	2.63	1.57
	103	0.76	3.02	2.37	1.70	0.56
	104	0.40	1.66	1.87	1.10	0.35
Mean		0.96	2.34	2.73	1.99	0.94
8	101	1.06	2.86	5.11	2.06	1.24
	102	1.14	4.57	4.67	2.08	1.14
	103	0.90	2.17	2.70	2.04	0.74
	104	0.26	2.84	1.98	1.01	0.37
Mean		0.84	3.11	3.62	1.80	0.87
10	101	2.00	2.19	3.20	2.48	1.11
	102	1.19	2.21	3.56	2.79	1.22
	103	0.82	0.60	1.08	2.42	0.79
Mean		1.00	1.67	2.61	2.56	1.04

[a] The initial dose was 1.50 g and then 0.5 g every 6 h for 10 days.
[b] NS, No sample.

apy in the four subjects who received a loading dose. In the 6-h josamycin group without a loading dose the mean concentrations at 0 and 6 h after day 2 ranged between 0.34 and 0.48 μg/ml. The higher mean peak and trough concentrations obtained with a loading dose were not due to subject variation. Three subjects participated in both studies (no. 3 = no. 102; no. 11 = no. 103; and no. 7 = no. 104). Their peak and trough plasma concentrations were consistently higher with the regimen that included a loading dose.

Josamycin concentration in urine, saliva, sweat, and tears. Mean concentrations in 24-h urine collections ranged between 195 and 465 μg/ml (Table 7). The urine recovery of an administered dose varied between 4.4 and 14.3% during the first 24 h. Between 168 and 192 h, the urinary recovery tended to be higher, ranging from 14.8 to 17.5%.

The concentration of josamycin in saliva, sweat, and tears was less than the mean peak plasma concentration, but it frequently exceeded the mean trough level (Table 8). Josamycin concentrations were highest in tear fluid, averaging 2.62 μg/ml. The mean concentration of josamycin was 1.03 μg/ml in saliva and 0.95 μg/ml in sweat.

Adverse reactions. No acute hematological, renal, or hepatic toxicity was observed with josamycin or erythromycin. There was no change in blood pressure or pulse determinations during therapy, and the miscellaneous blood chemistries were not influenced by either drug. Eosinophilia did develop in two subjects after 10 days of therapy with josamycin. The percentages of eosinophils after therapy were 7 and 8. A third subject started the 10-day study with 10% eosinophils and finished with 19% eosinophils. No other evidence of hypersensitivity was found in these subjects. Two had received josamycin before without developing eosinophilia.

Josamycin produced fewer side effects than did erythromycin stearate (Table 9). Only gastrointestinal side effects were recognized. Complaints of anorexia, mild epigastric discomfort relieved by food, or a change in stool characteristics was regarded as "mild" because it was not necessary to discontinue the study drug. Nausea with vomiting and diarrhea with abdominal cramps were considered to be "severe" side

TABLE 7. *Urinary excretion of josamycin*

Subject no.	Mean urine concn (μg/ml) at:		Urine recovery of administered dose (%) at:	
	0–24 h	168–192 h	0–24 h	168–192 h
101	465	410	7.4	17.1
102	293	370	14.3	17.5
103	276	380	7.3	14.8
104	195		4.4	

TABLE 8. *Josamycin concentration in saliva, sweat, and tears*

Fluid	No. of samples	Josamycin concn (μg/ml)	
		Mean ± standard deviation	Range
Saliva	10	1.03 ± 0.43	0.54–1.8
Sweat	7	0.95 ± 0.30	0.57–1.3
Tears	6	2.62 ± 0.72	1.8–3.6

TABLE 9. *Gastrointestinal side effects of josamycin and erythromycin therapy*

Drug	Regimen	No. of subjects	Dosage days	Dosage days with gastrointestinal complaints (%)		
				None	Mild[a]	Severe[b]
Josamycin	500 mg every 6 h × 4 days	21	84	92	8	0
Josamycin	500 mg every 8 h × 4 days	21	84	95	5	0
Josamycin	500 mg every 6 h[c] × 10 days	4	39	95	5	0
Erythromycin stearate	500 mg every 6 h × 4 days	7	24	50	29	21
Erythromycin stearate	250 mg every 6 h × 4 days	14	53	77	23	0

[a] Mild: anorexia, mild epigastric discomfort relieved by food, or change in stool characteristics.
[b] Severe: nausea with vomiting and/or diarrhea with abdominal cramps.
[c] Initial loading dose, 1.5 g.

effects, since withdrawal of the study drug was necessary. None of the subjects treated with josamycin had severe side effects. Only 5 of the 21 subjects in the 6-h josamycin group had mild gastrointestinal complaints, and these involved 8% of the dosage days. With the other two josamycin dosage schedules side effects were noted on only 5% of the dosage days. One subject in the 10-day study discontinued josamycin on day 9 because of malaise, abdominal cramps, and loose stools. These symptoms may not have been related to the drug, since the patient's wife and daughter had similar symptoms at that time. In contrast, the percentage of complaint days during the 4-day trials was significantly higher for the erythromycin groups than for the two josamycin groups ($P < 0.05$ by chi-square analysis). The 500-mg erythromycin stearate group experienced severe side effects on 21% of the dosage days and mild side effects on 29% of the dosage days. Five of the seven subjects in this group had complaints, and two were forced to stop therapy because of vomiting (one case) and diarrhea (one case). The 250-mg dose of erythromycin produced mild gastrointestinal side effects in 6 of the 14 subjects on 23% of the dosage days. One subject in this group stopped therapy on day 3 because of abdominal discomfort and borborygmus.

DISCUSSION

In general, josamycin compares favorably with erythromycin. It has a similar spectrum of bacteriostatic activity in vitro; however, josamycin is less potent by weight against most susceptible organisms. Concentrations of 0.5 μg/ml are effective in inhibiting all strains of *M. pneumoniae*, *S. pneumoniae*, *S. pyogenes*, and *N. meningitidis* (6, 7). A 2-μg/ml amount is required to inhibit the majority of strains of *S. aureus* and *B. fragilis* (6, 7).

In this study, the ranges of plasma concentrations of josamycin and erythromycin after equivalent oral dosages were similar. Subjects receiving erythromycin reached peak concentrations that were considerably higher than those of josamycin after the first dose (mean, 1.18 versus 0.61 μg/ml). However, the josamycin levels increased over the 4-day period, and mean concentrations on day 3 were higher than those achieved with erythromycin (2.31 versus 1.44 μg/ml). The tendency of josamycin to accumulate over the first 48-h of administration was also reflected in the trough levels. After an initial dose of 500 mg, the mean concentrations were 0.01 μg/ml at 6 h and 0 μg/ml at 8 h. However, trough concentrations after 48 h of drug administration reached a plateau of 0.34 μg/ml with the 6-h schedule and 0.09 μg/ml with the 8-h schedule. The gradual accumulation during the first 2 days of therapy prompted the second study in which a loading dose was used. The addition of the 1.5-g loading dose produced higher peak and trough plasma concentrations from the first dose onward.

Josamycin, like the other macrolide antibiotics, is metabolized rapidly in the liver to an inactive form and excreted primarily in the bile (6). Urinary excretion accounts for less than 20% of the elimination of the active form, but urine concentrations are high (200 to 400 μg/ml). The josamycin assay measured only biologically active drug and may not have detected inactive metabolites. In spite of these high urine levels, josamycin would probably not be of value for urinary tract infections since the vast majority of enterobacteriaceae are highly resistant to josamycin.

Josamycin was also detected in other body fluids in concentrations similar to those achieved in plasma. The concentration in sweat (mean, 0.95 μg/ml) and saliva (mean, 1.03 μg/ml) corresponded to plasma trough levels, and those in tears (mean, 2.62 μg/ml) corresponded to plasma peak levels. The levels in tears and saliva are considerably higher than those reported by Hoeprich (5) and others (3) with erythromycin. Hoeprich reported undetectable concentrations in saliva and 1 to 2 μg of drug per ml in tears (5). Concentrations of josamycin achieved in these secretions may, therefore, make it of value in the chemoprophylaxis of the meningococcal carrier state.

Josamycin was better tolerated in this study than was erythromycin stearate. At the higher dosage of erythromycin (500 mg every 6 h), five of seven subjects developed gastrointestinal symptoms, and it was necessary to stop the drug in two. This incidence of side effects was higher than that reported in previous studies (1, 2, 4), in which the drug was administered in lower dosages and usually not in a strictly fasting state. In the present study with the lower dosage of erythromycin stearate (250 mg every 6 h), complaints were milder but were still experienced in 23% of the dosage days. In contrast, josamycin produced mild side effects on only 5 to 8% of the dosage days. Therefore, it appears that josamycin was well tolerated, even in high dosages in a strictly fasting state. The comparison with erythromycin, however, must be interpreted with caution because the drugs were not administered in a blind fashion. No attempt was made to determine the influence of psychological factors on subjective complaints.

In conclusion, this new macrolide antibiotic provides comparable blood and urine concentrations to its analogue, erythromycin. Because it is well tolerated and it demonstrably penetrates into saliva, sweat, and tears, josamycin should be further studied to define its value in the therapy of clinical infections caused by *M. pneumoniae*, streptococci, staphylococci, and perhaps *Neisseria* species.

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