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Disposition of Phosphomycin in Patients with Pleural Effusion

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The pharmacokinetics of phosphomycin were studied in seven patients with pleural effusion of varied etiologies. All patients received a single intravenous bolus of 30 mg of antibiotic per kg. Phosphomycin levels in plasma and pleural fluid were determined simultaneously. Antibiotic levels in plasma followed a two-compartment open kinetic model. In the pleural fluid, maximum concentrations of phosphomycin, 42.63 ± 16.03 μg/ml (mean ± standard deviation), were reached at 3.69 ± 1.08 h after administration of the antibiotic. The disappearance constant of the antibiotic from the pleural fluid was significantly smaller (0.16 ± 0.06 h^{-1}) than the elimination constant determined from the levels of drug in plasma (0.73 ± 0.26 h^{-1}). Phosphomycin persisted in antibacterial concentrations in the pleural fluid for a considerable period of time. The low accessibility of phosphomycin observed in one of the patients in the study, with a maximum concentration value of 2.16 μg of phosphomycin per ml of pleural fluid, could be due to the existence of pachypleuritis in that patient; this was later confirmed in clinical and histological studies done after the research described here.

Phosphomycin, (−)-(1*R*,2*S*)-(1,2-epoxipropyl)phosphonic acid, is an antibiotic with a molecular weight of 138.1. It is not bound to proteins or biotransformed, and it is principally excreted through the kidney. Several studies have shown its activity against gram-positive and gram-negative organisms (7, 10, 11), and its clinical efficiency in the treatment of infections of the respiratory (2), gastrointestinal (14), and urinogenital (1) tracts has been demonstrated.

The determination of the levels reached by antibiotics in pleural fluid is of great interest due to the high number of secondary pleural effusions resulting from pulmonary infections (4, 5). This is, therefore, a determining factor in the treatment of infectious processes localized at this site. The aim of the present study was to establish the accessibility and persistence of an antibiotic such as phosphomycin in pleural fluid in circumstances in which it is necessary to achieve therapeutic concentrations in both pleural fluid and the pulmonary parenchyma, which will result in the eradication of the infectious process.

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MATERIALS AND METHODS

Patients. The pharmacokinetics of phosphomycin were studied in seven adult patients with pleural effusion, six male and one female, ranging from 54 to 85 years of age. None presented evidence of renal or hepatic pathology. Table 1 shows some of the clinical characteristics of the patients, including age, sex, weight, urea and creatinine concentrations in plasma, total proteins in plasma, volume of pleural fluid, total proteins in pleural fluid, and the cause of pleural effusion. The volumes of pleural fluid determined after extraction by continuous aspiration oscillated between 200 and 1,200 ml. All were transudate cases, with a protein content ≦3 g/dl. Informed consent was obtained from each patient before starting the study.

Antibiotic. Phosphomycin disodium was obtained from Compañia Española de Penicilina y Antibióticos, S. A. and Merck Sharp & Dohme (Spain).

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Administration of antibiotic and obtaining of samples. All patients received a single intravenous bolus dose of phosphomycin at 30 mg/kg. Antibiotic levels were determined simultaneously in plasma and pleural fluid. Samples of the latter were obtained by catheterization after direct pleural puncture. Samples of blood (treated with heparin) and pleural fluid were obtained at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after administration of the antibiotic, with additional samples taken at 0 and 0.25 h for blood. Blood samples were centrifuged, and the plasma was separated. Plasma and pleural fluid were frozen at −20°C until analysis.

Microbiological analysis. The concentrations of phosphomycin in plasma and pleural fluid were determined by a plate diffusion method with *Proteus vulgaris* MB-838 as the test organism (9). Calibration curves of phosphomycin were prepared in human plasma (concentrations from 200 to 6.25 μg/ml) and in human pleural fluid (concentrations from 100 to 6.25 μg/ml). Measurements were made in quadruplicate. The technique gave a standard error in its analysis of less than 8%; the sensitivity of the method was 1.50 μg/ml.

Pharmacokinetic analysis. The MAICE test (16) applied to experimentally determined concentrations of drug in plasma showed that a two-compartment open kinetic model provided the best estimate of the evolution of the drug levels in plasma. An iterative least-squares method was used to find the parameters for the rapid and slow disposition constants and the zero time intercepts for the concentration curve (13).

The penetration and disappearance of the antibiotic from pleural fluid followed first-order kinetic processes. An iterative least-squares method was used to find the parameters for the penetration and disappearance constants and the zero time intercepts for the penetration and disappearance phases. The remaining pharmacokinetic parameters were calculated from these values by the method of Wagner (15) with a Hewlett-Packard 85 computer.

RESULTS AND DISCUSSION

Tables 2 and 3 display the concentration of phosphomycin measured at various times after dosage in the plasma and pleural fluid of all patients included in the survey. Data on

TABLE 1. Clinical characteristics of patients included in the study

Patient no.	Sex	Age (yr)	Weight (kg)	Urea (mg/dl)	Creatinine (mg/dl)	Total proteins (g/dl)	Vol of pleural fluid (ml)	Total proteins in pleural fluid (g/dl)	Cause of pleural effusion
1	M	73	50.0	60	1.0	7.3	1000	3.0	Pulmonary neoplasm
2	M	62	57.0	40	0.9	6.8	700	2.5	Congestive heart failure
3	F	72	60.0	35	0.9	6.6	850	2.0	Congestive heart failure
4	M	70	80.0	43	0.9	7.4	500	2.8	Pneumonia
5	M	85	46.5	60	1.0	7.0	750	1.8	Congestive heart failure
6	M	54	67.0	42	0.9	8.2	1200	3.0	Pulmonary neoplasm
7	M	64	64.0	42	0.8	7.0	200	3.0	Pulmonary tuberculosis

patient 7 were excluded from calculation of mean concentrations. The low concentrations in the pleural fluid of this patient suggested the existence of some anomaly. The anomaly was later confirmed and is discussed below.

Tables 4 and 5 show the pharmacokinetic parameters of phosphomycin established from its concentrations in plasma and pleural fluid according to the pharmacokinetic model proposed.

The curve of the phosphomycin level in plasma has a biexponential plot characteristic of drugs that follow a two-compartment kinetic model. The level of the antibiotic fell from 350.2 μg/ml (the value of the concentration in plasma at zero time was obtained by extrapolation) to 59.6 μg/ml by 120 min after administration of the antibiotic, the moment at which the slow-disposition phase begins. The concentrations of drug in the plasma have a value of 5.9 ± 2.2 μg/ml (mean ± standard deviation) at 12 h after administration.

The plasma half-life of the slow-disposition phase ranged from 2.48 to 5.78 h. These values are greater than that of 1.91 h obtained in healthy volunteers receiving the same dose (6). Such differences may be partly attributable to the pulmonary disorders affecting the patients, together with the fact that most of the patients included in the study were elderly. The mean value found for the distribution volume of the antibiotic in the peripheral compartment was greater than that determined in the central compartment, although these differences are not statistically significant ($P > 0.05$). The clearance value of phosphomycin in plasma averaged 63.37 ± 11.18 ml/min, considerably less ($P < 0.05$) than that of 130.83 ± 52.89 ml/min found in healthy volunteers receiving the same dose (6). This difference could be ascribed to factors similar to those responsible for the difference in the slow-disposition phase half-lives. The ratio of the distribution constant for the central compartment to that of the peripheral compartment averaged 2.07, greater than that in healthy volunteers given the same dose (6).

In pleural fluid, a first phase may be observed in which the penetration processes predominate over those of elimination and in which an increase is seen in the concentrations reached by the antibiotic as a function of time, until a maximum value of 41.4 ± 16.6 μg/ml is reached at 3 h after administration of the antibiotic. From this moment on, the phosphomycin concentrations decrease as a result of the predomination of the disappearance processes over those of penetration, with a value of 15.4 ± 4.1 μg/ml at 12 h after administration of the drug.

The penetration of phosphomycin into the pleural fluid follows a first-order kinetic process, with an average value of 0.50 ± 0.13 h^{-1}, corresponding to an incorporation half-life of 1.48 ± 0.35 h. Figure 1 shows the linear relationship established between the phosphomycin concentrations in serum and pleural fluid once distribution equilibrium has been reached. This correlation, with a slope value of ca. 1, confirms the accessibility of the antibiotic to the pleural fluid.

The disappearance of the antibiotic from the pleural fluid showed values ranging between 0.25 and 0.08 h^{-1}, corresponding to a disappearance half-life ranging from 2.77 to

TABLE 2. Concentrations of phosphomycin in serum at various times after dosage

Patient no.	Micrograms of phosphomycin per milliliter of serum at hour after dosage:										
	0.25	0.50	1.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00
1	174.08	117.23	84.59	63.45	48.96	39.79	29.16	22.51	13.41	7.99	4.76
2	192.95	150.97	101.70	61.40	44.34	33.70	25.93	20.02	11.95	7.13	4.26
3	268.11	184.86	105.36	60.14	45.60	36.71	29.10	23.35	15.04	9.69	6.24
4	239.31	140.45	82.79	59.21	46.55	36.69	28.92	22.79	14.16	8.80	5.47
5	150.69	74.81	40.26	32.46	28.87	25.70	22.89	20.38	16.16	12.82	10.16
6	146.27	133.28	111.73	80.73	59.65	44.58	33.50	25.25	14.40	8.22	4.70
Mean	195.24	133.60	87.74	59.57	45.66	35.80	28.25	22.38	14.19	9.11	5.93
SD	49.17	36.61	25.96	15.50	9.91	6.14	3.57	1.95	1.43	2.01	2.19
7	139.60	82.49	56.14	36.53	24.08	15.87	10.46	6.89	2.99	1.30	0.57

TABLE 3. Concentrations of phosphomycin in pleural fluid at various times after dosage

Patient no.	Microgram of phosphomycin per milliliter of pleural fluid at hour after dosage:									
	0.50	1.00	2.00	3.00	4.00	5.00	6.00	8.00	10.00	12.00
1	14.18	27.10	49.86	44.76	43.51	39.80	35.13	25.79	18.15	12.52
2	21.05	33.31	45.29	47.67	45.43	41.20	36.25	27.12	19.70	14.16
3	3.51	8.89	16.26	20.41	22.45	23.14	22.97	21.25	18.82	16.31
4	13.85	20.43	29.05	33.42	35.07	35.03	33.95	30.29	26.04	21.98
5	9.03	17.33	27.99	33.13	34.79	34.32	32.60	27.54	22.15	17.35
6	25.60	49.50	68.83	68.76	61.13	51.41	41.94	26.65	16.47	10.07
Mean	14.54	26.09	38.05	41.36	40.40	37.48	33.82	26.44	20.22	15.40
SD	7.97	14.18	18.25	16.56	13.01	9.33	6.22	2.96	3.41	4.15
7		0.33	0.92	1.36	1.68	1.91	2.06	2.19	2.18	2.10

TABLE 4. Pharmacokinetic parameters obtained from the plasma levels of phosphomycin in each patient[a]

Patient no.	A_0 (μg/ml)	B_0 (μg/ml)	C_0 (μg/ml)	α (h^{-1})	β (h^{-1})	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{13} (h^{-1})	k_{12}/k_{21}	V_c (liters)	V_p (liters)	CL_P (ml/min)	$AUC_{0-\infty}$ (μg · h/ml)
1	239.90	106.48	339.37	4.57	0.26	0.15	2.67	2.48	1.60	0.73	1.54	4.42	6.81	54.11	462.06
2	160.67	94.10	254.67	1.71	0.26	0.41	2.67	0.62	0.80	0.56	0.78	7.85	6.12	72.69	458.57
3	322.49	87.42	409.91	2.22	0.22	0.31	3.15	1.04	0.65	0.76	1.60	4.39	7.04	55.25	542.95
4	400.00	95.05	495.05	3.93	0.24	0.18	2.89	2.23	0.95	0.99	2.35	4.85	11.43	79.81	501.16
5	339.97	40.88	440.85	4.48	0.12	0.15	5.78	3.08	0.52	1.00	5.92	3.18	18.47	52.82	441.73
6	26.00	135.15	161.15	1.00	0.28	0.69	2.48	0.08	0.88	0.32	0.25	12.41	13.52	65.52	508.72
Mean	247.01	93.18	350.20	2.98	0.23	0.32	3.27	1.59	0.90	0.73	2.07	6.18	10.61	63.37	485.87
SD	127.29	30.70	124.69	1.54	0.06	0.21	1.25	1.18	0.38	0.26	2.02	3.43	4.96	11.18	38.14
7	286.61	84.12	370.73	6.01	0.42	0.12	1.65	3.25	1.69	1.49	2.18	5.40	10.41	133.65	249.41

[a] Definitions of abbreviations for pharmacokinetic parameters are: A_0 and B_0, zero time intercepts for the concentration curve; C_0, concentration in plasma at zero time; α and β, rapid and slow disposition constants, respectively; $t_{1/2\alpha}$ and $t_{1/2\beta}$, plasma half-lives of the rapid and slow disposition phases, respectively; k_{12} and k_{21}, distribution constants of the central and peripheral compartments, respectively; k_{13}, elimination constant; V_c and V_p, apparent distribution volumes of the central and peripheral compartments, respectively; CL_P, plasma clearance; and $AUC_{0-\infty}$, area under the concentration-time curve, zero to infinity.

TABLE 5. Pharmacokinetic parameters obtained from the levels of the antibiotic in the pleural fluid of each patient[a]

Patient no.	A_i (μg/ml)	B_f (μg/ml)	K_i (h^{-1})	K_f (h^{-1})	$t_{1/2i}$ (h)	$t_{1/2f}$ (h)	C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-\infty(S)}/AUC_{0-\infty(PF)}$
1	141.15	136.53	0.51	0.20	1.36	3.52	44.80	3.05	1.11
2	105.77	108.17	0.60	0.17	1.16	4.10	47.69	2.94	0.99
3	48.68	45.32	0.39	0.08	1.78	8.35	23.14	5.01	1.29
4	65.09	70.35	0.40	0.10	1.73	7.30	35.18	4.70	0.87
5	101.67	99.77	0.38	0.14	1.82	4.92	34.83	4.13	1.00
6	217.37	203.28	0.69	0.25	1.00	2.77	70.14	2.30	1.02
Mean	113.29	110.57	0.50	0.16	1.48	5.16	42.63	3.69	1.05
SD	60.39	55.25	0.13	0.06	0.35	2.21	16.02	1.08	0.14
7	5.79	5.23	0.21	0.06	3.30	11.46	2.16	8.33	4.23

[a] Definitions of abbreviations for pharmacokinetic parameters are: A_i and B_f, zero time intercept for penetration phase and disappearance phase, respectively; K_i and K_f, penetration and disappearance constants, respectively; $t_{1/2i}$ and $t_{1/2f}$, pleural fluid half-lives of penetration and disappearance, respectively; C_{max}, maximum concentration of the drug in the pleural fluid; T_{max}, time at which C_{max} is reached; $AUC_{0-\infty(S)}/AUC_{0-\infty(PF)}$, ratio of $AUC_{0-\infty}$ in serum to $AUC_{0-\infty}$ in pleural fluid.

8.35 h. Consequently, the disappearance of the antibiotic from the pleural fluid is slightly slower than from the systemic circulation. These values obtained for the disappearance half-life of phosphomycin from pleural fluid are slightly greater than those recorded for some cephalosporins such as cefoxitin (4.83 ± 0.99 h) in similar studies (3), although the values of the elimination half-life of phosphomycin from the systemic circulation are also slightly greater than those corresponding to cefoxitin (1.46 ± 0.33 h) (3), but these differences are not statistically significant ($P > 0.05$).

Maximum phosphomycin concentrations in pleural fluid were ca. 40 μg/ml at 3 and 4 h after administration. This concentration is greater ($P < 0.05$) than those, found in pleural fluid under similar conditions, of cefazolin and cefotaxime, ca. 10 μg/ml (12); cefuroxime, >10 μg/ml (8); and cefoxitin, ca. 20 μg/ml (3).

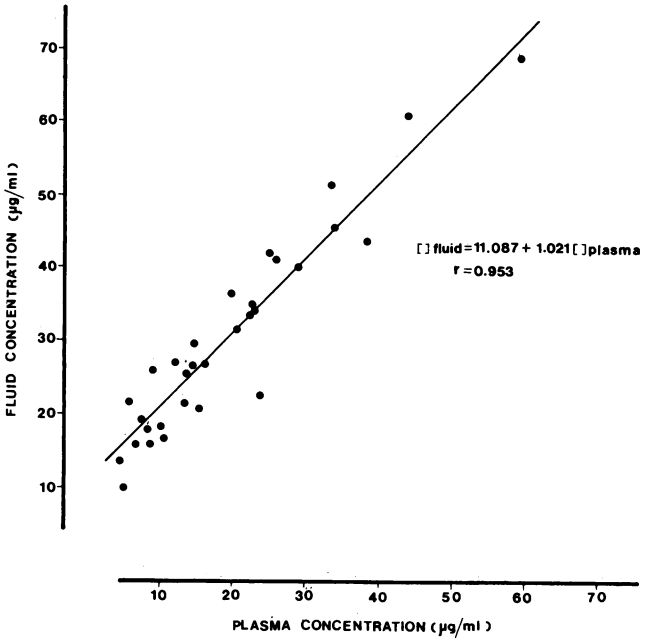

FIG. 1. Linear relationship between concentrations of phosphomycin in pleural fluid and plasma.

However, in one patient, the maximum concentration of phosphomycin reached in pleural fluid was 2.2 µg/ml at 8 h after administration (Fig. 2), and the pharmacokinetic parameters were seen to be different from those of the other patients included in the survey.

Clinical and histological studies carried out later by lung biopsy revealed the existence of pachypleuritis in this patient. Although not discarding the possible interindividual variations in the pharmacokinetics of the antibiotic, the poor accessibility of phosphomycin to pleural fluid in this patient could be attributed to the existence of such a pathological process; this should be the object of further studies.

Although large differences in the disposition processes of phosphomycin which were previously reported in experimental tissue fluid (6) have not been observed in this study of the evolution of antibiotic levels in plasma and pleural fluid, the lack of such differences could be attributed to certain characteristics of phosphomycin itself, such as its low molecular weight and the fact that it is not bound to plasma proteins. Further research is needed to confirm this aspect because, frequently, kinetic processes in plasma do not reflect drug kinetics in the different organs and tissues, due to the existence of individualized kinetic processes which are sometimes completely different.

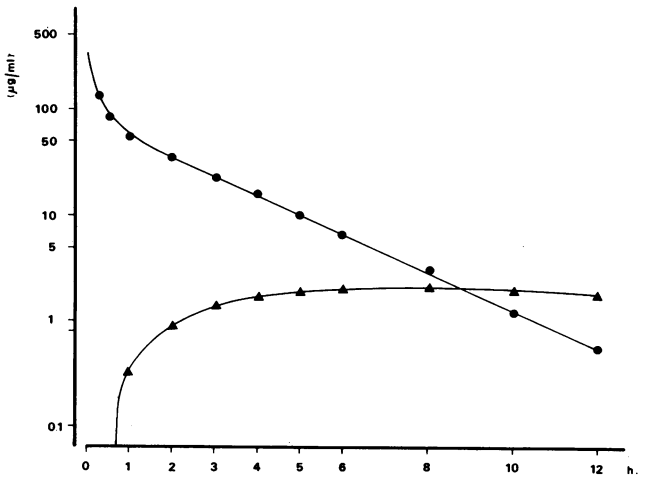

FIG. 2. Concentrations of phosphomycin in plasma (●) and pleural fluid (▲) of patient 7, affected with pachypleuritis.

The characterization of the pharmacokinetic profile of a drug from the values determined from its concentrations in plasma does not provide sufficient information regarding the evolution of the drug in different organs and tissues. This and the fact that patients with pleural effusion show the presence of a fluid which may be considered representative of interstitial tissue fluid (4) prompted us to carry out the study with the results discussed above.

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