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Pharmacokinetics and Bioavailability of Carbovir, a Carbocyclic Nucleoside Active against Human Immunodeficiency Virus, in Rats

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Carbovir is a novel carbocyclic nucleoside which has been shown to have potent in vitro activity against human immunodeficiency virus, the causative agent of acquired immunodeficiency syndrome. Sprague-Dawley male rats were used to investigate the pharmacokinetics and bioavailability of carbovir. Six rats received carbovir (20 mg/kg of body weight) through the jugular vein, and blood samples were collected through the femoral vein 2, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, and 240 min after the dose. Four of these rats also received a 60-mg/kg oral dose of carbovir, and a similar blood sampling schedule was followed. Whole-blood samples were prepared by solid-phase extraction, and the carbovir concentration in the samples was analyzed by reversed-phase high-pressure liquid chromatography. The profile of carbovir concentration in blood versus time after the intravenous dose was biexponential, with a very rapid distribution phase. Terminal elimination half-life was 21.4 ± 4.37 min, and total body clearance was 55.2 ± 13.8 ml/min per kg, which was within the range of the hepatic blood flow. The volume of distribution at steady state was 1,123 ± 250 ml/kg. The blood/plasma ratio and the plasma protein binding of carbovir in rat blood were determined in vitro by ultrafiltration. The plasma protein binding of carbovir was only 20% and was not concentration dependent. However, the blood/plasma ratio decreased significantly as concentration increased, indicating saturable binding sites in erythrocytes. After the oral dose, the terminal half-life was 81.0 ± 67.6 min, indicating that oral carbovir followed "flip-flop" kinetics, with absorption being much slower than elimination of the drug from the body. Oral bioavailability was 0.101 ± 0.035. Double peaks were present in the concentration-time profile for each rat receiving the oral dose, indicating either a delay in stomach emptying of the drug or slow dissolution of precipitated carbovir in the stomach and upper small intestine.

Carbovir (carbocyclic 2′,3′-didehydro-2′,3′-dideoxyguanosine; NSC-614846) is a novel carbocyclic guanosine derivative which has been shown to have potent in vitro activity against human immunodeficiency virus (6; R. Vince, M. Hua, J. Brownell, S. Daluge, F. Lee, W. M. Shannon, G. C. Lavelle, J. Qualls, O. Weislow, R. Kiser, P. G. Cannonico, R. Schultz, V. L. Narayanan, J. G. Mayo, R. H. Shoemaker, and M. R. Boyd, Biochem. Biophys. Res. Commun., in press). Carbovir inhibited human immunodeficiency virus replication and human immunodeficiency virus-induced cytopathic effects in human T-lymphoblastoid cells (lines ATH8, CEM, and MT-2) with a MIC for 50% of strains tested of 0.16 to 0.19 μg/ml. In contrast, cytotoxicity was observed at 50% inhibitory concentrations ranging from 35.0 to 60.5 μg/ml in the three cell lines (5a, 6). Because of its potential promise in the treatment of acquired immunodeficiency syndrome, the preclinical pharmacology and toxicology of carbovir are being investigated. This paper is the first report of the pharmacokinetics of carbovir in an animal model, Sprague-Dawley rats.

(Preliminary results of this work were presented at the Third Annual Meeting of the American Association of Pharmaceutical Scientists, 30 October to 3 November 1988, Orlando, Fla.)

MATERIALS AND METHODS

Chemicals. Carbovir and the internal standard for the high-pressure liquid chromatography (HPLC) assay, carbocyclic 2′,3′-dideoxyguanosine (Fig. 1), were synthesized by methods that will be reported elsewhere (R. Vince and M. Hua, submitted for publication). Triethylamine (gold label) was purchased from Aldrich Chemical Co., Inc. (Milwaukee, Wis.). HPLC-grade ammonium phosphate was obtained from J. T. Baker Chemical Co. (Phillipsburg, N.J.). HPLC-grade methanol and acetonitrile were obtained from Mallinckrodt, Inc. (Paris, Ky.). Heparin was obtained from Elkins-Sinn, Inc. (Cherry Hill, N.J.). All other chemicals were reagent grade or better.

Animals. Six male Sprague-Dawley rats (Bio-Labs, St. Paul, Minn.) weighing 300 ± 22 g (mean ± standard deviation) were used for the pharmacokinetic experiments. Intravenous cannulas were constructed from PE-50 tubing (Intramedic; Clay Adams, Parsippany, N.Y.) connected to Silastic (Dow Corning Corp., Midland, Mich.) tubing by a 23-gauge metal connector. Rats were anesthetized with sodium pentobarbital (50 mg/kg of body weight, intraperitoneally; Abbott Laboratories, North Chicago, Ill.), and the cannulas were surgically placed into the left jugular and femoral veins. The ends of the cannulas distal to the cannulation sites were tunneled subcutaneously to an opening at the nape of the neck, where they emerged and were placed into a spring tether (Harvard Bioscience, South Natick, Mass.), which was attached to the animal by means of an anchor button. A swivel-tether arrangement allowed free movement of the animal upon recovery from the surgery and during the drug studies. Food and water were allowed ad libitum.

Carbovir was dissolved in a solution containing normal saline and 1 equivalent of NaOH (pH 10) to a concentration of 10 mg/ml. One day after surgery, the rat received a

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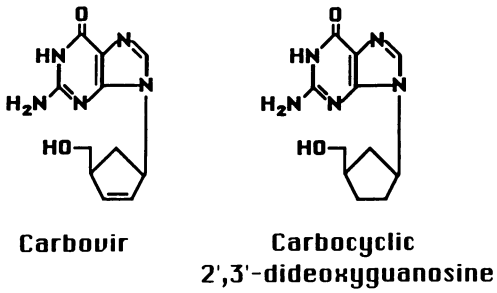

FIG. 1. Structure of carbovir and of the internal standard for the HPLC assay, carbocyclic 2',3'-dideoxyguanosine.

20-mg/kg dose of carbovir through the jugular vein. Blood samples (250 μl) were taken through the femoral vein cannula prior to dosing and 2, 5, 10, 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, and 240 min afterward. After 48 h, four of the rats received a 60-mg/kg oral dose via a stainless steel feeding needle. The same sampling schedule was used following the oral dose, but two additional blood samples were taken 300 and 360 min after the dose.

Assay. Carbovir was analyzed by a reversed-phase HPLC method preceded by solid-phase extraction of the whole-blood samples. Diluted whole-blood samples were applied to octadecysilane solid-phase extraction columns (Baker spe, 1-ml size; J. T. Baker) and were eluted with 60% methanol in water. The eluate was evaporated under N_2, reconstituted with the mobile phase, and injected onto the HPLC column. The analytical column was a 5-μm Adsorbosphere HS C_{18} cartridge (250 by 4.6 mm inside diameter) protected by a guard cartridge (10 by 4.6 mm) packed with the same material. The mobile phase consisted of 22% methanol–78% 0.01 M ammonium phosphate buffer containing 0.005 M triethylamine, pH 7.0. The flow rate was 1.0 ml/min, and the eluate was monitored at 252 nm. The lower limit of sensitivity of the assay was estimated to be 0.05 μg/ml. (A detailed description of the assay and its validation has been published elsewhere [R. P. Remmel, Y.-H. Yeom, M. Hua, R. Vince, and C. L. Zimmerman, J. Chromatogr. Biomed. Appl., in press].)

Blood-plasma distribution and protein binding. The blood/plasma ratio for carbovir and its plasma protein binding were determined in quadruplicate at three concentrations of carbovir in blood: 1, 5, and 10 μg/ml. A suitable volume of a standard solution of carbovir in methanol was placed into a screw-cap glass test tube and evaporated under nitrogen. Blood was obtained from the abdominal aortas of several rats anesthetized with ether. The blood was pooled, and the hematocrit was determined. Two milliliters of blood was placed into each tube, and the tubes were shaken (Labquake; Labindustries, Berkeley, Calif.) at approximately 8 cycles per min for 2 h at 37°C in an environmental room. Preliminary findings indicated that carbovir reached an equilibrium between plasma and erythrocytes within this period. After the 2 h, the blood was centrifuged and the plasma was removed. A 200-μl volume of each plasma sample was extracted by the solid-phase extraction method described above. The remainder of the plasma was bubbled with CO_2 to adjust the pH, and then 400 μl was placed into a Centrifree micropartition system (Amicon Corp., Danvers, Mass.) and centrifuged at 1,500 × *g* for 25 min at 37°C. The filtrate was extracted by the solid-phase extraction method, and the concentrations of carbovir in the plasma and the plasma filtrate were determined by comparison to an extracted standard curve of 0.625 to 10 μg/ml determined with plasma. The blood/plasma ratio was determined by dividing the spiked concentration of carbovir in blood by the measured concentration in plasma. The free fraction of carbovir in plasma was determined by dividing the concentration in the plasma filtrate by the measured concentration in plasma. The hematocrit was determined and the free fraction of carbovir in blood and the erythrocyte/plasma ratio were calculated as described by Gibaldi and Perrier (1). Analysis of variance with the procedure of Scheffé was carried out on the blood/plasma ratio, free fraction of carbovir in plasma and in blood, and erythrocyte/plasma ratio to determine whether these variables were concentration dependent. A P value of <0.05 was considered significant.

Pharmacokinetic analysis. The area under the concentration-time curve (AUC) was determined by the trapezoidal rule, with the area from the last measured concentration to infinity estimated as the last concentration divided by the estimated terminal elimination rate constant. The terminal elimination rate constant was determined by linear regression of the terminal portion of the concentration-time profile. The elimination-phase half-life was calculated by dividing 0.693 by the elimination rate constant. Total body clearance and the volume of distribution at steady state were calculated by a noncompartmental approach (1). Maximum concentration of carbovir in blood and the time in which this maximum was reached were determined by observation of the concentration-time profile. The concentration-time curve after the oral dose displayed "flip-flop" kinetics, so the terminal rate constant was assumed to be the absorption rate constant. The elimination rate constant after the oral dose was therefore determined by the method of residuals (1). The absorption-phase half-life was calculated by dividing 0.693 by the absorption rate constant. Oral bioavailability was determined by dividing the AUC after an oral dose by the AUC after an intravenous dose, corrected for the administered dose (1).

A compartmental analysis was also carried out on the concentration-time profile of carbovir in blood after an intravenous dose. The concentration-time data were fitted to a two-compartment model by PCNONLIN (5). The distribution-phase and elimination-phase half-lives and the volume of distribution in the postdistribution phase were calculated from the primary and secondary pharmacokinetic parameters generated by PCNONLIN. The volume of the central compartment was obtained directly from the PCNONLIN output.

Statistical comparisons of half-lives were made with the paired Student t test. A P value of <0.05 was considered significant.

RESULTS

With intensive sampling at early intervals after an intravenous dose, the concentration-time profile of carbovir displayed two-compartment pharmacokinetic characteristics. Figure 2A depicts the mean concentration-time profile in the six rats that received 20 mg/kg intravenously. The terminal elimination half-life was 21.4 ± 4.37 min (mean ± standard deviation), and total body clearance was 55.2 ± 13.8 ml/min per kg, indicating very rapid elimination. The results for the noncompartmentally derived pharmacokinetic parameters are given in Table 1. A standard two-compartment analysis was also carried out by using PCNONLIN to fit the individual profiles of carbovir concentrations in blood after an intravenous dose. The distribution-phase half-life

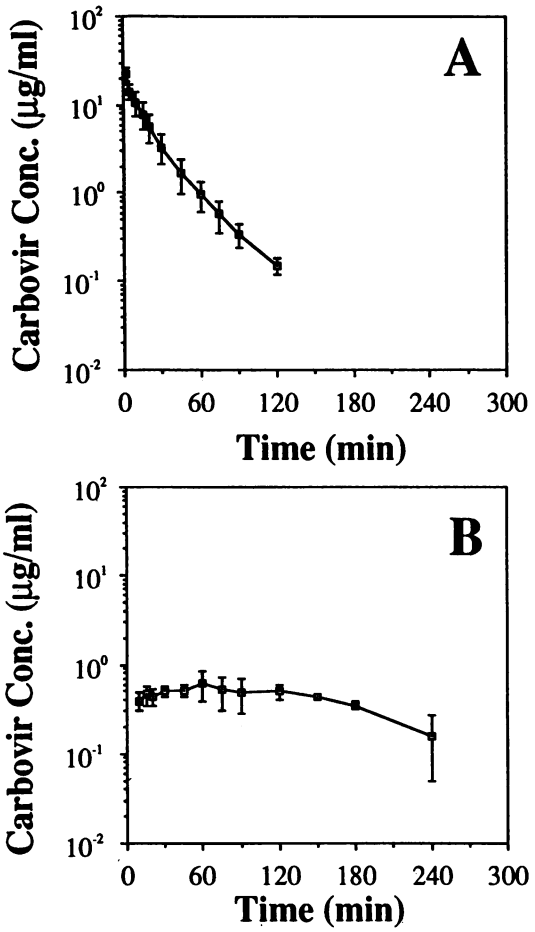

FIG. 2. Mean concentration-time data for the six rats that received carbovir (20 mg/kg) intravenously (A) and for the four rats that received carbovir (60 mg/kg) orally (B). Error bars represent standard deviations.

was very rapid (4.9 ± 4.9 min), with a slower terminal elimination-phase half-life (15.6 ± 2.9 min) (Table 2). There was no significant difference among the elimination half-lives, whether determined compartmentally or noncompartmentally.

Rat A was administered a 20-mg/kg oral dose; carbovir was almost undetectable in the blood of this animal. The next four rats therefore received 60-mg/kg oral doses of carbovir. Table 3 presents pharmacokinetic data obtained after oral dosing of carbovir. The terminal half-life after an oral dose was 81.0 ± 67.6 min. Since the elimination half-life after an intravenous dose appeared to be considerably shorter, the terminal half-life after the oral dose was considered the absorption half-life, thus indicating flip-flop kinetics. Figure 2B depicts mean data for the four rats and clearly shows that the terminal phase was longer than that for rats given intravenous carbovir (Fig. 2A). An estimate of the elimination half-life obtained by the method of residuals was not significantly different from the elimination half-life determined from the data for rats receiving intravenous carbovir. In all of the rats receiving oral carbovir, double peaks in the concentration-time profile were observed. This led to considerable variability in the estimates of the maximum carbovir concentration and of the time when this was reached (Table 3). Figure 3 shows the concentration-time profiles in rat B after oral and intravenous dosing; the double peaks after the oral dose are more clearly seen than in the presentation of mean data. Oral bioavailability was 0.101 ± 0.035.

Table 4 presents the results of the study of equilibration of carbovir in blood and plasma protein binding. The blood/plasma ratios for carbovir at 5.0 and 10.0 μg/ml (1.16 ± 0.067 and 1.11 ± 0.027, respectively) were significantly lower than that for carbovir at 1.0 μg/ml (1.35 ± 0.052). The erythrocyte/plasma ratios followed the same pattern. While the free fraction of carbovir in plasma did not change over the concentration range studied, the free fraction in blood was significantly higher at 5.0 and 10.0 μg/ml (0.692 ± 0.070 and 0.735 ± 0.026, respectively) than at 1.0 μg/ml (0.605 ± 0.046). Although three of the four parameters showed significant differences when results for carbovir at 1.0 μg/ml were

TABLE 2. Compartmentally derived pharmacokinetic data on carbovir in rats after a single intravenous dose

Rat	$t_{1/2\beta}$[a] (min)	$t_{1/2\alpha}$[b] (min)	V_c[c] (ml/kg)	V_β[d] (ml/kg)
A	12.6	1.2	359	1,438
B	14.1	1.7	644	1,013
C	15.1	1.2	326	1,066
D	16.1	5.2	804	1,024
E	14.7	13.9	947	978
F	21.0	6.4	864	2,165
Mean ± SD	15.6 ± 2.9	4.9 ± 4.9	657 ± 263	1,281 ± 465

[a] $t_{1/2\beta}$, Elimination-phase half-life.
[b] $t_{1/2\alpha}$, Distribution-phase half-life.
[c] V_c, Volume of the central compartment.
[d] V_β, Volume of distribution in the postdistribution phase.

TABLE 1. Noncompartmental pharmacokinetic data on carbovir in rats after a single intravenous dose

Rat	Dose (mg/kg)	$t_{1/2}$[a] (min)	AUC (μg · min/ml)	CL[b] (ml/min per kg)	V_{ss}[c] (ml/kg)
A	20.5	29.9	271.4	75.6	1,619
B	20.4	18.1	424.5	48.0	993
C	20.6	22.1	410.4	50.1	1,072
D	20.2	19.3	470.4	42.9	952
E	20.4	19.3	450.2	45.3	987
F	20.6	19.6	296.3	69.6	1,117
Mean ± SD	20.4 ± 0.15	21.4 ± 4.37	387.2 ± 83.1	55.2 ± 13.8	1,123 ± 250

[a] $t_{1/2}$, Elimination-phase half-life.
[b] CL, Total body clearance.
[c] V_{ss}, Volume of distribution at steady state.

TABLE 3. Pharmacokinetic data on carbovir in rats after a single oral dose

Rat	Dose (mg/kg)	$t_{1/2}$[a] (min)	$t_{1/2abs}$[b] (min)	AUC (μg · min/ml)	C_{max}[c] (μg/ml)	T_{max}[d] (min)	F[e]
B	58.3	23.2	45.9	125.2	0.96	59.4	0.103
C	61.8	15.9	182.4	184.3	0.54	77.0	0.149
D	61.4	30.5	49.3	107.6	0.57	30.3	0.075
E	59.4	33.0	46.5	99.6	0.50	20.6	0.076
Mean ± SD	60.2 ± 1.66	25.6 ± 7.7	81.0 ± 67.6	129.2 ± 38.3	0.64 ± 0.21	46.8 ± 26.0	0.101 ± 0.035

[a] $t_{1/2}$, Elimination-phase half-life.
[b] $t_{1/2abs}$, Absorption-phase half-life.
[c] C_{max}, Maximum concentration of carbovir in blood.
[d] T_{max}, Time in which the maximum concentration of carbovir in blood was reached.
[e] F, Oral bioavailability.

compared with those for carbovir at 5.0 or 10.0 μg/ml, there were no significant differences among variables when the 5.0-μg/ml data were compared with the 10.0-μg/ml data.

DISCUSSION

Carbovir is undergoing extensive preclinical testing to ascertain its usefulness as a treatment of acquired immunodeficiency syndrome. Like other nucleosides, such as 3′-azido-3′-deoxythymidine (AZT) and 2′,3′-dideoxycytidine (DDC), carbovir is rapidly removed from the body after an intravenous dose (2, 3). In humans, the total body clearance of AZT is approximately 1.3 ± 0.3 liters/h per kg, a value which approaches that of hepatic blood flow, and the terminal elimination half-life is 1.1 ± 0.2 h (3). In BFD_1 mice, the total body clearance of DDC is 30.5 ml/min per kg, with a terminal elimination half-life of 69 min (2). The total body clearance of DDC is 9.6 to 11.8 ml/min per kg in the rhesus monkey, with an elimination half-life of 102 to 114 min (2). The total body clearance of carbovir, 55.2 ± 13.8 ml/min per kg, is within the range of liver blood flow in rats (40 to 60 ml/min per kg), but as with other high-clearance compounds, the liver may be only one of several potential sites of elimination. If the terminal elimination half-life of carbovir in humans is similar to that in rats (21.4 min), then intravenous drug administration will most likely be done by continuous infusion. It must be noted, however, that the elimination of xenobiotics by rats and mice is generally more rapid than in humans (4). The volume of distribution of carbovir at steady state indicates considerable distribution outside the vascular space, as noted for AZT (3).

Although the plasma protein binding of carbovir was concentration independent over the range of carbovir concentrations in plasma observed in the present study, the distribution into and binding within erythrocytes appeared to be concentration dependent. As the concentration of carbovir in blood increased, the free fraction in blood increased significantly and the erythrocyte/plasma and blood/plasma ratios decreased. Saturable binding within the erythrocytes is a likely explanation. In this study, in which whole blood was assayed and pharmacokinetic observations were based on blood data, the saturable binding in blood was of little kinetic consequence. However, in future clinical studies, in which the biological fluid assayed is likely to be plasma or serum, the interpretation of plasma pharmacokinetic data must be approached cautiously. Since blood is the medium perfusing the eliminating organs, concentration-dependent changes in carbovir distribution within the blood might lead to changes in the disposition of the compound. These changes would not be immediately apparent from the plasma data, since plasma protein binding appeared to be independent of concentration. On the other hand, if carbovir is a compound with a high extraction ratio with respect to the liver, its clearance would be dependent only on hepatic blood flow, and changes in blood binding might be of little concern. Until more is known about the site(s) of elimination, the most conservative approach would be to analyze whole blood in pharmacokinetic studies.

If hepatic or intestinal wall clearance of carbovir was largely responsible for the total body clearance, then the low oral bioavailability could have been due to first-pass metabolism as well as to the lack of absorption from the gastrointestinal tract. Absorption of carbovir from the gastrointestinal tract was slow, contributing to the observed bioavailability of approximately 10%. Comparison of the concentration-time profiles after oral and intravenous administration indicated that absorption of carbovir from the gastrointestinal tract was slower than its elimination from the body. A similar absorption profile was reported for DDC in mice, in which oral bioavailability was 20 to 30% (2). AZT was reported to have a bioavailability of 63 ± 13% in humans (3). Since AZT may be a high-clearance drug with respect to the liver, the higher bioavailability may indicate that it is better absorbed from the gastrointestinal tract than is either DDC or carbovir. AZT is more lipophilic than carbovir, as

TABLE 4. Blood/plasma ratios and binding of carbovir in rat blood[a]

Carbovir concn in blood (μg/ml)	Blood/plasma ratio	Free fraction of carbovir in:		Erythrocyte/plasma ratio
		Plasma	Blood	
1.0	1.35 ± 0.052	0.813 ± 0.037	0.605 ± 0.046	1.82 ± 0.123
5.0	1.16 ± 0.067[b]	0.806 ± 0.050	0.692 ± 0.070[b]	1.39 ± 0.157[b]
10.0	1.11 ± 0.027[b]	0.789 ± 0.027[c]	0.735 ± 0.026[b,c]	1.27 ± 0.075[b]

[a] For all concentrations, $n = 4$ unless noted otherwise. Results are presented as means ± standard deviations.
[b] Significantly different from value for carbovir at 1 μg/ml ($P < 0.01$, analysis of variance [Scheffé procedure]).
[c] $n = 3$.

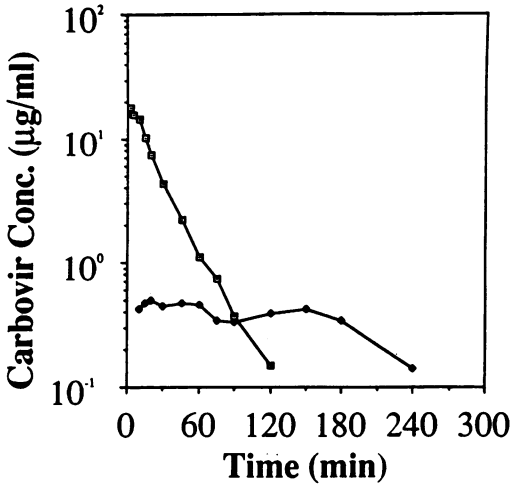

FIG. 3. Concentration-time profiles for rat B after receiving intravenous carbovir (20 mg/kg) (⊡) and oral carbovir (60 mg/kg) (◆).

indicated by its capacity factor determined in a reversed-phase HPLC assay (Remmel et al., in pres), and the greater lipophilicity of AZT may contribute to its enhanced oral bioavailability.

For each rat receiving oral carbovir, double peaks were observed in the concentration-time profile. It is unlikely that the peaks were due to enterohepatic recycling, since the absorption from the gastrointestinal tract is relatively low and reabsorption of recycled drug would not contribute significantly to the drug concentration in the blood. More likely explanations for the double peaks include delayed stomach emptying or erratic dissolution of precipitated carbovir. To diminish potential effects on metabolism, the rats were not subjected to fasting prior to the oral dosing, and food in the stomach may have contributed to the delayed emptying into the small intestine. In a comparison of DDC absorption in fasting and nonfasting mice, a slightly higher bioavailability was observed in the nonfasting animals, which was attributed to decreased gastrointestinal motility resulting from the presence of food (2). Alternatively, the carbovir may have precipitated from the alkaline medium in which it was administered when it entered the acidic environment of the stomach and upper intestinal tract. Subsequent dissolution may have been slow and erratic. If the absorption of carbovir is inherently poor because of its lack of lipophilicity, delaying stomach emptying or dissolution may provide a means of enhancing overall absorption.

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