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Hemodialysis Clearance of Intravenously Administered Ribavirin

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A patient with an implanted artificial heart, acute, anuric renal failure, and disseminated influenza virus type A infection received intravenous ribavirin. Drug elimination by hemodialysis was measured. Plasma dialysis clearance averaged 93.9 ± 8.6 ml/min. The maximum amount of ribavirin removed from the body during one period of hemodialysis was 79.1 mg. Ribavirin is not removed in important quantities by hemodialysis.

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) has been used in an aerosol preparation for the treatment of infections caused by influenza type A and B virus strains (5, 6, 8, 12). It has also been given intravenously as therapy for Lassa fever (9). Recently, results of pharmacokinetic studies of the intravenous formulation were published (7), but more information is necessary to determine proper dosage under various clinical circumstances. We report findings in a patient treated with intravenous ribavirin for disseminated influenza virus type A (H1N1) infection complicating an artificial heart implantation and anuric renal failure.

Full details of the patient's clinical history have been published separately (10). At the time of these studies, the patient was a 40-year-old woman who weighed 65 kg. She had undergone an artificial heart implant (Jarvik 7-70) 4 days previously, and she was severely ill with documented disseminated influenza virus type A infection as well as acute, anuric renal failure, respiratory failure, and severe obtundation. Ribavirin therapy commenced following written, informed consent by the family and approval by our human subject review committee. Hemodialysis was begun 13 h later and resulted in prompt reductions in blood urea nitrogen and creatinine. Over the succeeding weeks, renal function improved and the patient's condition stabilized. She died 8 months after this episode, of unrelated medical complications.

Ribavirin was provided by Viratech, Inc. (Costa Mesa, Calif.). The intravenous preparation was administered as a loading dose of 2 g and then 1 g 1 h following the completion of each hemodialysis period. All doses were given over 30 min via an infusion pump. During the course of treatment, hemodialysis was performed on days 1, 2, 4, 5, 7, 8, and 9 with a Travenol regenerated cellulose-acetate system and on day 6 with a Travenol cuprophan system. Vascular access was obtained via femoral arterial and central venous lines. Blood flow was maintained at 175 ml/min on days 1, 2, and 4 and 200 ml/min on days 5 and 6. Dialysate flow rate was 500 ml/min. Blood samples were obtained as follows. A single sample was drawn immediately prior to the beginning of each hemodialysis period. One to three pairs of arterial and venous samples (inflow and outflow) were drawn during each dialysis run. Additional samples were usually obtained 2.5 and 8 h after the beginning of each ribavirin infusion. Blood (3 ml) was drawn from an indwelling arterial line and placed in heparinized tubes. Samples were then immediately centrifuged, and plasma was separated from erythrocytes. Both plasma and erythrocytes were frozen and stored at −70°C until analysis. Ribavirin concentrations in plasma were determined by a radioimmunoassay method described previously (1). Ribavirin concentrations in erythrocytes were determined by the same method, after 1,000-fold dilution of the packed erythrocytes with distilled water. Standard curves for erythrocyte ribavirin determinations were made up in the same media, i.e., 1,000-fold dilutions of drug-free erythrocytes in water.

Dialysis clearance was calculated by using the concentrations determined in the paired arterial and venous blood samples taken during dialysis. An extraction ratio (ER) was calculated for each arterial-venous concentration pair by the relationship $ER = (C_a - C_v)/C_a$, where C_a and C_v are the arterial and venous ribavirin concentrations in plasma, respectively. Plasma flow rate was calculated by multiplying the blood flow rate by the quantity (1 − Hct/100), where Hct is the patient's hematocrit (percent). Plasma ribavirin dialysis clearance was calculated as the product of the extraction ratio and plasma flow rate (4). The amount of ribavirin removed during dialysis was calculated as the product of the dialysis clearance (in milliliters per minute), the duration of dialysis (in minutes), and the arterial concentration of ribavirin at the midpoint of the dialysis period (micromolar).

Hemodialysis was performed seven times with a cellulose-acetate regenerated column (days 1, 2, 4, 5, 7, 8, and 9). On day 1, one determination of dialysis clearance and extraction ratio yielded values of 88.9 ml/min and 0.72, respectively. Two determinations on day 2 gave clearances of 99.4 and 89.2 ml/min and extraction ratios of 0.80 and 0.72. On day 4, a single determination gave a clearance of 87.3 ml/min and an extraction ratio of 0.68. Three determinations on day 5 yielded clearances of 81.4, 110.6, and 94.2 ml/min and extraction ratios of 0.64, 0.81, and 0.69. For cellulose-acetate columns, the mean clearance and extraction ratio (plus or minus standard deviation) were 93.9 ± 8.6 ml/min and 0.72 ± 0.06, respectively. On day 6, dialysis was performed with a cuprophan column. Three measurements of dialysis clearance and extraction ratio gave means (plus or minus standard deviation) of 56.4 ± 2.2 ml/min and 0.40 ± 0.02, respectively. The amounts of ribavirin removed by

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hemodialysis on days 2, 4, 5, and 6 were 41.5, 52.1, 68.2, and 79.1 mg, respectively.

On two occasions, pairs of concentrations in plasma were obtained which met reasonable criteria for calculation of interdialysis half-life; that is, they were taken in the postdistributive period (at least 8 h after dosing), no further dosing or dialysis occurred between the two samples, and the samples were separated by ≥12 h in time. From these, a mean interdialysis half-life of 25.7 h was estimated. Obviously this is a suboptimal estimate; a sampling period of three to four times the length of the half-life would be preferred. Unfortunately, a longer interval could not be obtained because of the necessity of daily dialysis and other clinical interventions. A crude estimate of distribution volume, made by using a single concentration obtained 9 h after the loading dose, was 482 liters. Although these estimates represent only rough approximations, they agree reasonably well with previously published values for ribavirin (3, 7). Plasma ribavirin clearance in this patient, based on these values, was approximately 217 ml/min.

Ribavirin levels in erythrocytes were measured 12 times during the patient's course of treatment. The mean level (plus or minus standard deviation) was 1,109.2 ± 146.6 μM (range, 880 to 1,334 μM). Ratios of ribavirin concentration in erythrocytes to ribavirin concentration in plasma averaged 38.8 ± 9.2, demonstrating extensive partitioning of ribavirin into erythrocytes. This ratio is higher than that determined by Laskin and co-workers (7); however, the ratios reported here were not determined in a closed system and obviously do not represent true partition coefficients. The major adverse effect of this drug has been anemia in monkeys (2) and in humans (9, 11). This patient's hemoglobin remained constant, and free plasma hemoglobin levels were not altered by treatment. No other overt signs of toxicity were noted.

It has been postulated that ribavirin dosing regimens do not need to be changed in renal failure, as less than 40% of the drug is excreted unchanged in the urine in 3 days (7). However, it is important to know the effects of hemodialysis on plasma ribavirin clearance so that interdialysis dosing can assure adequate therapeutic levels. The plasma clearance of ribavirin was 93.9 ± 8.6 ml/min during hemodialysis with a regenerated cellulose-acetate column and 56.4 ± 2.2 ml/min with a cuprophan column. The maximum amount of ribavirin removed during any one period of dialysis was 79.1 mg, which represents approximately 8% of the 1-g maintenance dose this patient received after each period of dialysis. Depending on the type of column used, total plasma clearance of ribavirin during dialysis was increased by only 26 to 43% over the estimated interdialysis value of 217 ml/min. These calculations demonstrate that hemodialysis had minimal effect on the total body mass of ribavirin in this patient.

More work is necessary to better define the pharmacokinetics of ribavirin in renal failure. We have learned from this patient that ribavirin, while readily extracted from plasma, is not cleared from the body in important quantities by intermittent hemodialysis. This is consistent with previously reported pharmacokinetic characteristics of ribavirin (7). What effects other forms of dialysis, such as continuous arteriovenous hemodialysis or peritoneal dialysis, might have on ribavirin clearance remain to be determined, but it appears unlikely that these effects will be important; generally, neither method is more efficient than hemodialysis in removing drugs from the blood. On the basis of these data, administration of additional ribavirin to replace that removed by hemodialysis appears unwarranted. However, because of the significant extraction ratio for plasma (0.4 to 0.72, depending on the column used), it may be appropriate to withhold dosing of ribavirin until each dialysis is completed, rather than administering it immediately before or during the procedure.

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