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Distribution characteristics of mitoxantrone in a patient undergoing hemodialysis

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Summary. The pharmacokinetic profile of mitoxantrone in a patient undergoing hemodialysis is described. Significant characteristics of our patient included lymphoma with liver involvement, tumor lysis syndrome, renal and hepatic failure. Combination chemotherapy consisted of mitoxantrone, vincristine, and cyclophosphamide. Mitoxantrone plasma samples were obtained prior to dosing and at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.5, 7.0, and 12 h after the intravenous infusion of a 17-mg dose over 20 min. Serum concentrations were determined by high-performance liquid chromatography. The serum concentration versus time curve was consistent with a three-compartment model. However, rebounds in serum drug concentrations were detected during the last portion of dialysis and after its completion. The gamma elimination half-life could not be determined due to the continued detection of rebounds in drug concentrations throughout the postdialysis sampling period. The alpha and beta distribution phases did not appear to be affected by hemodialysis. The peak mitoxantrone concentration fell within the reported range. Mitoxantrone does not appear to be eliminated by hemodialysis, and dose adjustments are not needed in patients undergoing this procedure.

Introduction

Extensive reviews of mitoxantrone pharmacokinetics and metabolism appear in the literature [6, 11] but no information about its behavior in the setting of hemodialysis has been published. We describe a patient with advanced lymphoma, tumor lysis syndrome and renal failure, who was dialyzed and concurrently treated with mitoxantrone. Serum mitoxantrone concentrations were measured during the first 12 h after drug infusion including four hours of hemodialysis. These results show that mitoxantrone is not removed by dialysis, but that rebound serum concentration may persist longer than that which would be expected.

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Case report

A 71-year-old woman (height, 162.6 cm; weight 50 kg; body surface area 1.52 m^2) was admitted for treatment of massive hepatomegaly, splenomegaly, and ascites. The patient had been well until 2 weeks prior to admission, at which time she developed a tender spleen, malaise, and nausea. A computed tomographic (CT) scan of the abdomen showed that the liver was diffusely enlarged. A focal abnormality was also noted on ultrasound and was thought to be a hemangioma. The spleen was enlarged and displayed heterogeneous areas of low density, consistent with lymphoma. Ascites and a right pleural effusion were seen. No involvement of the kidneys or ureters was noted. At admission, the patient's hematocrit was 42, her WBC was $43.5 \times 10^3/mm^3$, and her platelet count was $259 \times 10^3/mm^3$. Other laboratory findings included the following: calcium, 10.4 mg/dl; blood urea nitrogen (BUN), 76 mg/dl; creatinine, 1.8 mg/dl; uric acid, 25.5 mg/dl; bilirubin 9.3 mg/dl; alkaline phosphate, 1,455 IU/l; lactic dehydrogenase (LDH) 6,758 IU/l; chloride, 89 mEq/l, and anion gap, 23. A bone marrow biopsy revealed 40% replacement by lymphocytes, which stained positive with the pan B-cell marker L-26. Emergency intravenous chemotherapy was begun at 36 h after admission and consisted of 650 mg/m^2 cyclophosphamide, 10 mg/m^2 mitoxantrone, 1.5 mg vincristine, and hydrocortisone. Renal dialysis was also started because of hyperkalemia, rising levels of BUN and creatinine, and markedly elevated uric acid, consistent with tumor lysis syndrome. Dose modifications were not made because the hepatic abnormalities were believed to be disease-related.

At 4 days after the administration of chemotherapy, the patient became leukopenic (total WBC, $3.1 \times 10^3/mm^3$). Her WBC had dropped to $0.4 \times 10^3/mm^3$ by the 8th day posttreatment, at which point she developed *Pseudomonas aeruginosa* septicemia. The WBC nadir occurred on day 9 ($0.3 \times 10^3/mm^3$; 4% segmented neutrophils and band forms). On the 10th day posttreatment, the patient's WBC was $0.8 \times 10^3/mm^3$, with 47% of the cells being segmented neutrophils and band forms. On the 11th day posttreatment, the patient died of *Pseudomonas* sepsis in spite of maximal antibiotic and supportive care. No autopsy was performed.

Serum mitoxantrone concentrations were obtained at 0, 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.5, 7.0, and 12.0 h after the i. v.

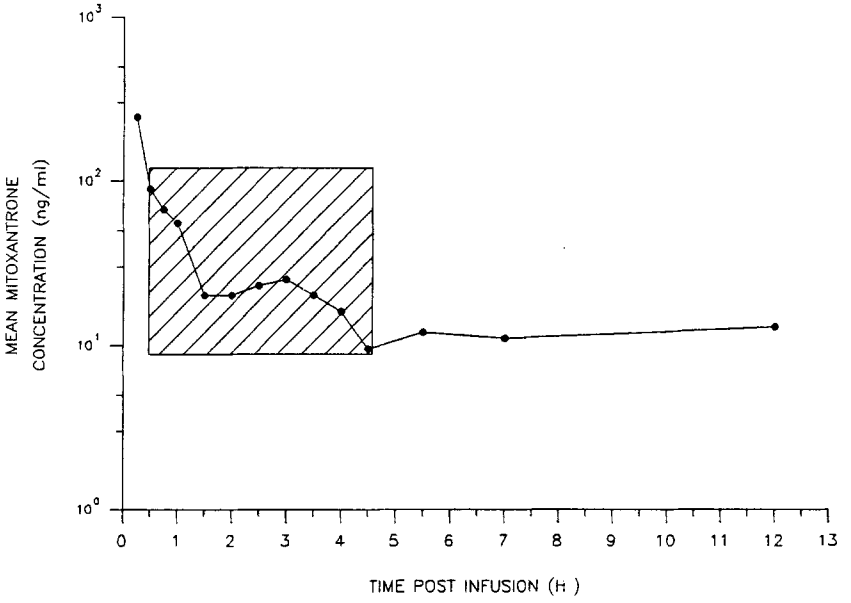

Fig 1. 0–12 hour mitoxantrone serum concentration vs time curve for a patient undergoing hemodialysis. The hatched area represents the time of dialysis.

Fig. 1. The 0- to 12-h mitoxantrone serum concentration versus time curve generated for a patient undergoing hemodialysis. The *hatched area* represents the dialysis period

infusion of a 17-mg dose over 20 min. Hemodialysis was started at 30 min postdosing and was continued for 4 h. Blood samples were collected in specimen tubes in the absence of coagulant, and the serum was separated after the blood had clotted. Citrate buffer was added to each sample for stabilization, and the samples were frozen at –40° C until analysis [10].

Mitoxantrone was isolated in duplicate by solid-phase extraction. Each preparatory column (PrepSep-C18, Fisher Scientific) was preconditioned with 5 ml methanol followed by 10 ml water. Plasma (1 ml) was applied, and after a 2-ml water wash, the mitoxantrone was eluted with 500 µl 0.5 *N* methanolic hydrochloric acid. Concentrations were determined by high-performance liquid chromatography [3]. The mobile phase, consisting of 75% 0.05 M ammonium formate (pH 3.0) and 25% acetonitrile, was run at a flow rate of 1 ml/min. Then, 100 µl sample was injected onto a C18 (30 cm × 10 mm) reverse-phase column (Waters Associates, u-Bondapak) and UV detection was performed at 658 nm. The sensitivity was set at 0.002 absorbance units full scale (AUFS), with the response time being 0.5 s. The lower limit of detection for this procedure was 2 ng/ml. Intra-day coefficients of variation were 8% at 500 ng/ml and 7% at 5 ng/ml. Each sample was assayed in duplicate, and the mean concentration was used to construct the serum concentration versus time curve.

The serum concentration versus time curve was visually inspected for model characteristics. Distribution constants were calculated by hand according to the method of residuals as previously described [6].

Results

The 0- to 12-h concentration curve was consistent with a three-compartment profile (Fig. 1). The peak plasma concentration fell within the range previously reported by other investigators [3, 10, 12] and was followed by a rapid alpha distributive phase ($t_{1/2}$, 5 min). The 0.5- to 1.5-h serum concentrations declined at a rate similar to that reported for the mitoxantrone beta distribution phase ($t_{1/2}$, 0.47 h). At 2 h into the hemodialysis procedure, slight rebounds in plasma drug concentrations were detected. This phenomenon continued for 1 h, with mitoxantrone concentrations continuing to decline for the last 1.5 h of hemodialysis at a rate consistent with the beta distribution ($t_{1/2}$, 1.1 h). After the completion of hemodialysis, serum concentrations began to rebound for the remainder of the sampling period. The greatest extent of rebound occurred during the 1st h postdialysis. No serum drug concentration was detected at between 7 and 12 h after dialysis, and none was found after 12 h for the further characterization of gamma elimination.

Discussion

Visual inspection of the serum concentration versus time curve revealed that probable hemodialysis-induced fluid shifts resulted in alterations in mitoxantrone concentrations that were not attributable to normal distribution and elimination processes. These changes diminished the utility of pharmacokinetics-modeling computer programs in detailing the physiologic behavior of mitoxantrone in this patient.

Extensive reviews of mitoxantrone pharmacokinetics and metabolism have appeared in the literature [5, 11]. In summary, mitoxantrone follows a triphasic pattern of decline in serum concentration, with wide interpatient variations occurring in pharmacokinetic indices. The alpha half-life ranges from 4.1 to 10.7 min, the beta half-life range is 0.3–3.1 h, and the gamma elimination half-life is 10–40 h. This type of pharmacokinetic behavior suggests deep-tissue compartment penetration in association with slow release.

Pharmacokinetic parameters, including gamma elimination and total plasma clearance, are affected by organopathy. Our patient exhibited clinical and diagnostic evidence of ascites and severe hepatic dysfunction, which are known to alter mitoxantrone clearance and toxicity patterns. Savaraj et al. [12] have observed a terminal half-life increase to 53.5–173.2 h in patients presenting with

third spacing or hepatic dysfunction. Although the initial distributive phase was prolonged, the serum concentrations were fit to a two-compartment model. Smyth et al. [13] have also reported observing an terminal half-life of 62 h in a jaundiced patient. The alpha and beta distributive phases did not appear to be affected by organ dysfunction or third space. This was again confirmed by our analysis.

The principle dose-limiting toxic side effect of mitoxantrone and mitoxantrone-containing regimens is myelosuppression, which primarily involves granulocytopenia. In early clinical trials, dose reductions were necessary in a majority of patients [4, 8]. Chlebowski et al. [2] have outlined variations in the clinical course of hyperbilirubinemic patients receiving mitoxantrone. Hyperbilirubinemic patients with hepatocellular carcinoma experienced fewer hematologic toxic events than did similar patients with breast cancer. Abnormal indocyanine green clearance was associated with increased granulocyte depression, suggesting potentiation of mitoxantrone toxicity with decreasing hepatic blood flow.

The time to nadir WBC in our patient lay within the range expected to result from mitoxantrone combination therapies. On the 10th day posttreatment, the total WBC began to increase, as did the percentage of segmented neutrophils and band forms. Unfortunately, because the patient died so soon after treatment, it is difficult to judge from a clinical standpoint as to whether her course would have involved a more prolonged neutropenia than would normally be expected.

In our study, renal failure did not appear to alter the elimination of mitoxantrone. The principle factor that influenced serum drug concentrations is believed to be hemodialysis-induced rebound. Other medications have produced rebound phenomena during and following hemodialysis [1, 9, 14]. Postdialysis increases in serum drug concentrations usually occur within the 1st h after the procedure and are attributable to a redistribution of drug from the tissue into the plasma [7]. The postdialysis mitoxantrone levels in our patient rose most dramatically during the 1st h following the completion of the procedure. However, the 12-h level also appeared to be attributable to the rebound effect; for this reason, the gamma elimination half-life could not be calculated. Continuation of plasma sampling beyond the original 12-h period would have enabled the quantitation of the gamma elimination value.

It is our belief that rebounds in mitoxantrone concentrations occurred as a result of drug sequestration in peripheral tissue due to blood-flow alterations as a consequence of hemodialysis. On the normalization of hemodynamic conditions at dialysis completion, a release of drug from those sites forced reequilibration. This phenomenon and the resultant inability to calculate the gamma half-life has been demonstrated elsewhere [15]. Redistribution of mitoxantrone from ascitic fluid is also possible. Since the intravascular space is acutely contracted during hemodialysis, reequilibration of fluid from the peritoneal cavity to the central compartment would create a transfer gradient for mitoxantrone. Serial determinations of mitoxantrone concentrations in ascitic fluid during hemodialysis would help to confirm this hypothesis. However, this procedure was too invasive for our single-patient analysis. Since only 6%–10% of the delivered dose of mitoxantrone is recovered in the urine at ≥ 24 h, dose adjustment in view of renal failure is unnecessary.

We can only speculate as to the mechanism of rebound during the dialysis procedure. Perhaps hemodynamic normalization began toward the later part of the dialysis period. It is unlikely that assay variability played a significant role in the increasing serum concentrations. The within-day coefficient of variation at the lower end of detection was only 8%, which does not account for the entire elevation in concentration. Alternative methods for the detection and confirmation of drug removal by means of dialysate capture would be of little value, since the quantity of mitoxantrone present in a large dialysate volume would be far below the limits of chromatographic detection.

In conclusion, mitoxantrone is not removed by dialysis; however, a rebound phenomenon occurs. The rebounds in serum drug concentrations may persist beyond the periods normally expected and may contribute to increased toxicity potential. It is unknown whether prolonged rebounds in mitoxantrone concentrations or levels of any of the concomitantly infused chemotherapeutic agents or of their combination led to the excessive myelosuppression observed in our patient. Additional studies in dialysis patients showing no evidence of severe hepatic involvement are needed to elucidate this point. Further evaluation of mitoxantrone's dialyzability during the gamma elimination phase is also indicated.

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