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Toxicity, pharmacokinetics, and in vitro hemodialysis clearance of ifosfamide and metabolites in an anephric pediatric patient with Wilms' tumor

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Abstract *Purpose:* We evaluated the in vitro hemodialysis ratio and subsequent toxicity and pharmacokinetics of ifosfamide in an anephric patient with Wilms' tumor. *Methods*: An in vitro model was used to determine the extraction ratio of ifosfamide by dialysis. The toxicity and plasma concentrations of ifosfamide, chloroacetaldehyde, and 4-hydroxyifosfamide were then determined over 24 h after a single 1.6 g/m^2 dose of ifosfamide. Plasma concentrations were also measured before and after ten dialysis sessions during four courses of ifosfamide therapy. *Results*: The in vitro hemodialysis model showed that ifosfamide was cleared with an extraction ratio of 86.7 ± 0.5% and remained constant even at low concentrations of drug. The mean decrease in vivo following hemodialysis for ifosfamide, chloroacetaldehyde, and 4-hydroxyifosfamide were 86.9%, 77.2%, and 36.2%, respectively. The pharmacokinetic parameters for ifosfamide using model-independent methods were calculated: Vd = 0.23 l/kg, $t_{½}$ = 4.8 h, and Cl_T = 3.30 l/h per m^2. Ifosfamide-associated neurotoxicity was noted within hours of drug administration and improved rapidly following hemodialysis. *Conclusions*: The results of our study suggest that the pharmacokinetics of parent ifosfamide may not be substantially altered in patients with renal failure. Hemodialysis was shown to remove ifosfamide, chloroacetaldehyde, and 4-hydroxyifosfamide from the blood stream. Hemodialysis was also shown to reverse ifosfamide-related neurotoxicity.

Key words Ifosfamide · Pharmacokinetics · Pediatrics · Hemodialysis · Wilms' tumor

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Introduction

Ifosfamide, a member of the oxazaphosphorine family of alkylating agents, has shown efficacy as a single agent in the treatment of several types of recurrent or refractory pediatric solid tumors [1–10]. This agent is currently combined with other antineoplastic agents including etoposide and cisplatinum or carboplatinum [11–14]. These studies have shown that ifosfamide-based regimens are particularly effective in the treatment of patients with relapsed or persistent Wilms' tumor [1–8, 11–13]. However, its use in refractory disease is usually limited by nephrotoxicity and is frequently associated with decreased renal function following prior chemotherapy with cisplatinum or previous unilateral nephrectomy [7, 15]. Limited data with cyclophosphamide in patients with renal failure and in the anuric patients would suggest that the dose of ifosfamide be reduced in patients with renal compromise [16–18]. However, there are no reported data on the use of dialysis or the pharmacokinetics of ifosfamide, alone or in combination with other agents, in patients with renal failure.

We report here laboratory studies that determined the extraction ratio of ifosfamide using hemodialysis. In addition, ifosfamide toxicity as well as pharmacokinetics, and efficacy of hemodialysis of ifosfamide, chloroacetaldehyde (CAA), and 4-hydroxyifosfamide (4HI) in the treatment of Wilms' tumor in an anephric patient are discussed.

Materials and methods

Patient

A 20-month old child presented to the Children's Medical Center of Dallas with a history of abdominal fullness and hypertension. Further evaluation and tissue biopsy revealed bilateral Wilms' tumor of favorable histology. The patient was treated with weekly doses of vincristine and pulses of dactinomycin. In addition, radiation therapy was given to both kidneys. Upon completion of therapy, surgical re-exploration revealed persistent tumor, now of unfavorable histology. After bilateral nephrectomies, the patient was begun on ifosfamide and dialysis, although there was no measurable disease to follow response to therapy. Pending the toxicity profile of single-agent ifosfamide, the addition of etoposide and carboplatinum was anticipated.

Chemotherapy

Ifosfamide was administered as a single agent every 3 weeks over 30 min for a total of four courses. Table 1 lists details of dose, schedule, and toxicities encountered with each course. Based upon the presence or absence of toxicities seen with each dose of ifosfamide, subsequent courses were adjusted as to dose, schedule, and total number of doses delivered per course of therapy. Other medications concurrently administered during the study included digoxin, for the treatment of cardiomyopathy, ranitidine, ondansetron, and metoclopramide.

Pharmacokinetics

Specimens for ifosfamide, CAA, and 4HI determinations were obtained over a 24-h period before, during and after a single 30-min infusion of ifosfamide given in course 1. In addition, samples were obtained for analysis before and after dialysis following each dose of therapy. Specimens were also obtained from peritoneal dialysate at hour 25 of course 1.

All samples were frozen immediately and stored at −70 °C until shipped on dry-ice to St. Jude Children's Research Hospital for analysis. Ifosfamide and CAA concentrations were determined within 12 days by gas chromatography using thermionic-specific [19] and electron capture detection [20], respectively. 4HI was determined by high-pressure liquid chromatography [21] based on the method of Alarcon et al. [22].

Standard curves consisting of at least six calibrator concentrations, and duplicate sets of control samples at low, middle, and high concentrations, were prepared in normal donor plasma for analytical assays of patient samples and in dialysis buffer for the in vitro model. Ifosfamide and 4HI were obtained from Asta Medica, and CAA was prepared by distillation from a 50% solution obtained from Pflatz & Bauer. The lower limits of quantitation were 1 μM, 1 μM, and 1.5 μM, and the between-assay ($n > 5$) coefficients of variation of the standards and controls were less than 10.4%, 12.9%, and 8.5%, for the ifosfamide, 4HI, and CAA assays, respectively. Baseline resolution was observed for the measured analytes relative to unidentified chromatographic peaks in uremic plasmas.

Pharmacokinetic calculations

The computer program Rstrip II (version 2.2; MicroMath Scientific Software, Salt Lake City, Utah) was used to fit data obtained from predialysis plasma sampling for ifosfamide, CAA, and 4HI and for calculation of the pharmacokinetic parameters. The AUC was calculated using the Lagrande/polynominal procedure. The predialysis plasma samples at 4, 6, 12, and 24 h were used to estimate the half-life ($t_{½}$). The following formulas were used to estimate the total clearance (Cl_T) and the initial volume of distribution (Vd) of ifosfamide:

Table 1 Ifosfamide dosing, schedule, and associated toxicities (*T* tremor, *Se* sedation, *I* irritability, *A* ataxia, *Sz* seizure, *A* absolute neutrophil count per mm^3, *P* platelet count × 1000 per mm^3)

Course	Dose	Dose/day (g/m^2)	Interval between doses (h)	Start of Dialysis (hours from end of dose)	Toxicity		
					CNS	Hematologic	
						Start	Nadir
1	1	1.6		24	T, Se, I	A 12 284 P 344	A 1368 P 82
2	1	1.6	72	7	Se	A 25 200 P 219	
	2	1.0		7	Se, A		A 440 P 23
3	1	1.0	48	7	Se	A 12 482 P 235	
	2	1.0	48	7	Se, I		
	3	1.0		7	Se		A 1173 P 59
4	1	1.0	24	7		A 9490 P 160	
	2	1.0	24	7			
	3	1.0	24	7			
	4	1.0	24	7	T, Se, I		A 414 P 5
	5	–[a]			Sz		

[a] No dose given owing to development of seizure activity

$Cl_T = Dose/AUC$

$Vd = Dose/k_{el} \times AUC$

k_{el} = elimination constant

In vitro dialysis

An in vitro model was designed to establish extraction ratios for ifosfamide during dialysis and consisted of a Toray $B_{2.0}$ 0.5 filter and neonatal tubing. The arterial and venous lines of the circuit were connected to a container filled with phosphate-buffered saline (140 m*M* NaCl, 5 m*M* KCl, and 10 m*M* Na_2HPO_4; pH 7.4) with a volume equal to the patient's Vd for ifosfamide. A dose of 800 mg ifosfamide (equal to the original dose of ifosfamide received by the patient) was added to the buffered saline and mixed continuously. Dialysis was initiated matching conditions of dialysis in the patient. Pre- and postfilter samples for the measurement of ifosfamide levels were obtained at 0, 15, 30, 60, 120, 180, and 240 min. The extraction ratio was calculated using the equation:

$$\text{Extraction ratio} = \frac{\text{Prefilter concentrations} - \text{Postfilter concentrations}}{\text{Prefilter concentrations}} \text{ (expressed as a percent)}$$

The pre- and postfilter ifosfamide concentrations were fitted by exponential curves. The amount of ifosfamide removed by hemodialysis could then be calculated as the area between these curves multiplied by the blood flow rate (see Appendix).

In vivo dialysis

The patient was initially started on peritoneal dialysis; however, because of inadequate peritoneal catheter function, hemodialysis was instituted before therapy with ifosfamide was started. Hemodialysis was performed using a Toray $B_{2.0}$ 0.5 filter with blood flow rates of 50–75 ml/min. The length of time on dialysis was between 233 and 266 min.

Results

Table 1 summarizes the ifosfamide dosing schedule and associated toxicities observed with each course of chemotherapy. A single 1.6 g/m^2 dose over 30 min of ifosfamide was given in course 1 followed by 3.5 h of dialysis at hour 24. Following course 1, dialysis was performed 6–7 h after each dose. The dose of ifosfamide was 1.6 g/m^2 for the first dose of course 2; all subsequent doses of ifosfamide were 1 g/m^2. Dosing intervals were either 72 h, 48 h, or 24 h.

Sedation occurred with seven of ten doses of ifosfamide (Table 1). Irritability, tremor, and ataxia were occasionally observed. These toxicities were noted within hours of completion of drug infusion and improved promptly with hemodialysis. Seizure activity was seen during the patient's fourth course of therapy approximately 28 h after completion of four daily 1 g/m^2 doses of ifosfamide and four daily dialysis sessions. Ifosfamide, CAA, and 4HI concentrations were detectable before, during, and after the time of seizure activity, but at plasma concentrations near or below the limit of quantitation for their respective assays. The serum potassium and bicarbonate concentrations at the time of the seizure were 4.6 meq/l and 27 meq/l, respectively. The serum albumin during the first three courses of ifosfamide was between 2.0 and 3.0 g/dl.

Hematologic toxicities included leukopenia, decreased absolute neutrophil count (ANC), and thrombocytopenia (Table 1). The degree of thrombocytopenia seen with each dose appeared to correlate with the total number of doses of ifosfamide delivered per course of therapy. The nadir for platelet count occurred 10–11 days following the initiation of each course. Platelet counts had recovered (platelet count > 100 000/mm^3) by 12–22 days following initiation of chemotherapy. Fever and sepsis were not encountered. Nadirs for white cell count and ANC occurred 8–10 days following the start of chemotherapy, with recovery (ANC > 500) between days 11 and 12.

The manifestation of seizure activity associated with course 4 of therapy was considered dose-limiting and further therapy was discontinued. The patient died approximately 2 months after the last dose of ifosfamide; no autopsy was obtained. Prior to the patient's death, aspiration of a peritoneal fluid collection confirmed the presence of viable tumor.

The pharmacokinetic relationships of blood concentrations of ifosfamide, CAA, and 4HI with time were derived from data collected during the first course of therapy (Fig. 1). A model-independent method was used to determine pharmacokinetic parameters. The $t_{1/2}$ for ifosfamide was 4.8 h. The area under the concentration time curve (0–∞ AUC), Cl_T, and Vd for ifosfamide were 9251 μ*M* h, 3.30 l/h per m^2, and 0.23 l/kg, respectively. The concentration of 4HI remained stable following the 30-min infusion of ifosfamide, achieving a peak blood concentration of 6.42 μ*M* and an AUC of 783.9 μ*M* h. The blood concentration-time curve for CAA appeared less stable, reaching a peak concentration of 14.83 μ*M* at 4 h following the end of ifosfamide infusion. The AUC for CAA was 1817.2 μ*M* h following the first course of ifosfamide. The AUC for the metabolites,

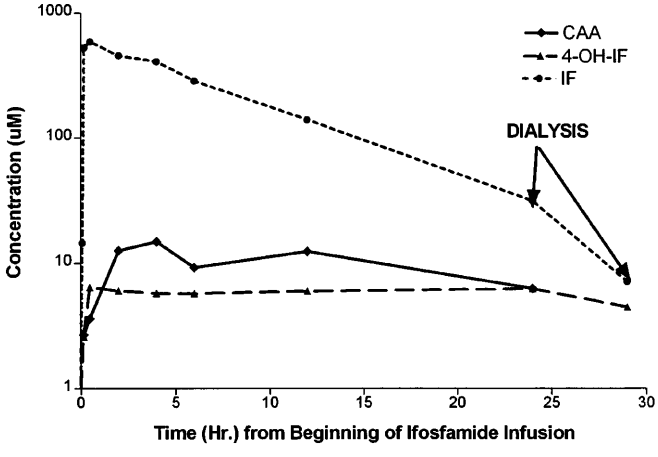

Fig. 1 Ifosfamide, chloroacetaldehyde, and 4-hydroxyifosfamide concentrations following intravenous infusion of 1.6 g/m^2 ifosfamide over 30 min

Table 2 Concentrations (μM) of ifosfamide and metabolites pre- and posthemodialysis. Dialysis was performed 24 h postifosfamide administration for course 1 only; for all other courses dialysis was performed at 6–7 h postifosfamide administration

	Ifosfamide			4-Hydroxyifosfamide			Chloroacetaldehyde		
	Pre	Post	decrease (%)	Pre	Post	decrease (%)	Pre	Post	decrease (%)
Course 1									
Dose 1	31.8	7.2	77.4	6.3	4.5	28.7	6.3	< 1.5	
Course 2									
Dose 1	157.0	30.9	80.3	5.2	3.2	38.2	20.2	6.6	67.3
Dose 2	72.1	12.2	83.1	4.5	2.6	41.4	19.9	4.9	74.9
Course 3									
Dose 1	94.6	12.6	86.7	2.2	1.6	27.3	11.4	2.6	77.4
Dose 2	66.3	7.1	89.4	3.2	1.9	40.6	14.5	1.8	87.6
Dose 3	66.7	6.8	89.8	3.3	2.1	36.8	13.6	3.1	77.0
Course 4									
Dose 1	96.8	13.8	85.7	1.8	1.5	16.4	8.2	2.3	71.4
Dose 2	92.5	8.0	91.3	3.7	1.8	51.3	10.3	2.1	79.6
Dose 3	61.4	4.6	92.5	4.4	3.2	27.5	11.1	2.6	76.1
Dose 4	65.0	4.5	93.1	5.1	2.3	54.0	15.0	2.5	83.6
Mean			86.9			36.2			77.2
SD			5.3			11.5			6.0

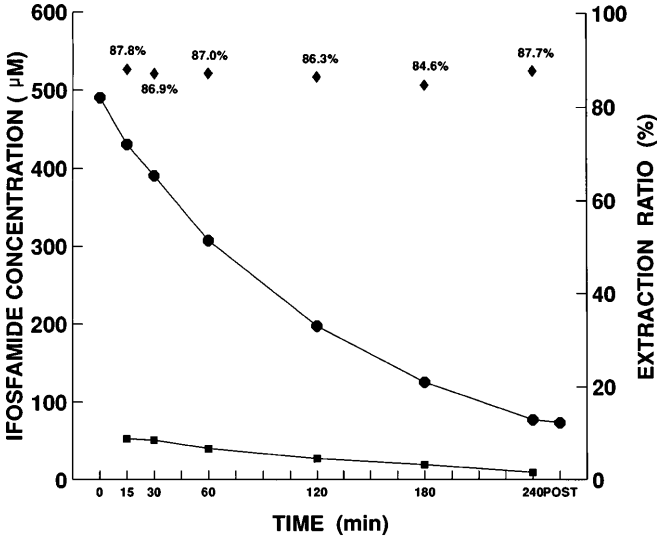

Fig. 2 Ifosfamide clearance through the dialyzer in an in vitro model (● predialyzer concentration, ■ postdialyzer concentration ◆ extraction ratio)

expressed as a percent of the AUC for ifosfamide, were 8.5% and 19.6% for 4HI and CAA, respectively.

The in vitro hemodialysis model showed that ifosfamide was cleared with an extraction ratio (mean ± SEM) of 86.7 ± 0.5% that remained constant even at low concentrations of drug (Fig. 2). Applying these kinetic parameters to each of the patient's hemodialysis sessions would predict a mean (± SEM) decrease in the patient's ifosfamide blood concentrations of 83.8 ± 0.4% per session if no ongoing metabolism occurred. Based upon the actual concentrations of ifosfamide at the start of dialysis and the calculated Vd, the mean (± SEM) predicted absolute amount of drug removed during hemodialysis would be 100.1 + 13.1 mg (39.5–194.3 mg; see the Appendix for details).

Removal of ifosfamide, CAA, and 4HI by hemodialysis during each course of chemotherapy for this patient is illustrated in Table 2. The mean (± SD) decrease in blood concentrations following dialysis for ifosfamide, CAA, and 4HI were 86.9 ± 5.3%, 77.2 ± 6.0%, and 36.2 ± 11.5%, respectively. The actual contribution of dialysis to changes in ifosfamide, 4HI, and CAA concentrations would have to take into account concurrent ongoing metabolism of parent drug and metabolites. For example, based on a $t_{1/2}$ of 4.8 h, the actual decrease in ifosfamide, secondary to dialysis, would be approximately 50%. For courses in which more than one dose of ifosfamide was given, there was no apparent accumulation of parent compound. In addition, during courses 1–3 there was no apparent accumulation of either 4HI or CAA with each dose. However, during course 4 there was an increase in predialysis concentrations of 4HI (1.8 → 5.1 μM) and CAA (8.2 → 15.0 μM) over the four doses of ifosfamide.

While no peritoneal dialysis was performed during ifosfamide therapy, abdominal fluid (312 ml) was removed using the peritoneal catheter 24 h following the first dose (course 1) of ifosfamide and analyzed for parent drug and CAA. The concentration of ifosfamide and CAA was 33.5 μM and 3.18 μM, respectively.

Discussion

Several recent studies on the pharmacokinetics of ifosfamide in children have been reported and are summarized in Table 3. In these studies, ifosfamide was administered as either a 72-h infusion or as a 1-h or 3-h bolus to children with normal renal function [23–28].

Table 3 Pharmacokinetic parameters of ifosfamide in children

Reference	Schedule	*n*	$t_{½}$ (h)	Cl_{Total}(l/h/m^2)	Cl_{Renal}(l/h/m^2)	Vd(l/kg)	GFR(ml/min/1.73 m^2)
23	9 g/m^2 over 72 h	11	2.06 ± 0.78	6.38 ± 2.96		0.68 ± 0.38	126.1 ± 38.1
24	3 g/m^2 over 1 h	17	4.73 ± 2.31	3.81 ± 1.08		0.81 ± 0.24	134.3 ± 32.8
24	9 g/m^2 over 72 h	17	2.07 ± 0.72	5.48 ± 2.68		0.67 ± 0.39	132.7 ± 33.5
25	9 g/m^2 over 72 h	21		3.27 ± 2.57			
26	2 g/m^2 over 1 h	2	2.93, 5.10	2.12, 2.76			
26	3 g/m^2 over 3 h	1	2.10	8.89			
26	9 g/m^2 over 72 h	2	4.20, 3.80	4.03, 3.93			
27	9 g/m^2 over 72 h	16	2.12 ± 0.92	5.04 ± 1.66	0.66 ± 0.38	0.58 ± 0.23	127.2 ± 35.6
Present study	1.6 g/m^2 over 0.5 h	1	4.80	3.30		0.23	

For children receiving ifosfamide by bolus administration, the pharmacokinetic parameters of parent compound appeared similar to those observed in this study. Since initial metabolism of ifosfamide is mediated by the cytochrome P450 enzyme CYP3A4 [29, 30], the impact of renal failure on ifosfamide pharmacokinetics may be limited. However, it should also be noted that renal elimination of ifosfamide in children has been estimated to be between 5 and 34% [27, 28, 31, 32] of the administered dose. The pharmacokinetics of parent cyclophosphamide in adults with renal failure do not appear to be substantially altered compared to patients with normal kidney function [16–18]. Direct comparison with other studies is complicated by other factors such as concurrent medications, age, and differences in dosing regimens and methods of pharmacokinetic parameter analysis.

Because of the multitude of metabolites and limited data on the fate of ifosfamide metabolites in children, particularly 4HI, determining the impact of renal failure on metabolite pharmacokinetics is difficult. Since renal excretion of 2- and 3-dechloroethylated ifosfamide in children has been shown to account for between 15 and 31% of the administered ifosfamide dose, it must be assumed that renal failure would impact on the pharmacokinetics of ifosfamide metabolites [31, 32]. Studies with cyclophosphamide in adults with renal insufficiency have shown that accumulation of some metabolites does occur when compared to individuals with normal kidney function [16–18]. In an anuric patient given cyclophosphamide, accumulation of alkylating metabolites has been reported [16]. In this study, following the initial administration of ifosfamide, a peak concentration of 14.8 μM at 4 h for CAA was observed followed by an apparent decline in blood concentrations. Compared to an earlier study in children given ifosfamide, using a similar dosing regimen, the concentrations of CAA observed in this patient appeared to be less [33]. However, compared to adults given 1.5 g/m^2 of ifosfamide, the peak concentration of CAA observed in this study was three- to sevenfold higher [34].

Autoinduction of ifosfamide metabolism has been previously reported in children [23–26]. The process of autoinduction in children can be seen in as little as 6 h after the start of ifosfamide infusion [25]. In this study, with limited data and differences in dosing regimens it is difficult to determine whether autoinduction occurred in this patient. There was an apparent decline during course 4 in predialysis concentrations of ifosfamide with subsequent doses of drug, suggesting that autoinduction occurred. It has also been observed in adult patients that concurrently with autoinduction of ifosfamide metabolism, concentrations of 4HI and CAA metabolites in the blood increase [34]. Predialysis concentrations of 4HI and CAA remained stable during the first three courses of ifosfamide administration in this patient, but a consistent increases in both 4HI and CAA predialysis concentrations were also noted with each dose of ifosfamide administration during course 4. While autoinduction may explain the apparent increase in metabolite formation in course 4, the impact of renal failure on possible accumulation of 4HI and CAA must also be considered. Lastly, the considerable amount of intrapatient variability that has been observed with autoinduction may also contribute to the difficulty in interpreting the above results [25].

A previous report has shown that hemodialysis is effective in removing cyclophosphamide and its metabolites in patients with renal failure [16]. For this patient, hemodialysis appeared to be an effective mechanism for removing ifosfamide and CAA from the blood stream. The removal of 4HI by hemodialysis appeared to be less efficient. It should be noted that the impact of plasma protein binding on ifosfamide extraction in vitro was not evaluated in this study. However, plasma protein binding of ifosfamide appears to be limited [35]. The data obtained from the peritoneal dialysate, while suggesting this mode of dialysis may also be effective in removing ifosfamide and its metabolites, is too limited to support any conclusions.

Hemodialysis also resulted in improvement of sedation, tremors, ataxia, and irritability seen during and after ifosfamide therapy. This patient did experience seizure activity more than 24 h after the last ifosfamide dose of course 4 but had no further seizure activity following dialysis. The toxicities observed occurred at substantially lower plasma concentrations of CAA than previously associated with neurotoxicity in children [33]. The neurotoxicity from ifosfamide in this patient may have resulted from an unidentified metabolite, from tissue accumulation of CAA, or a combination of these factors. It should be noted that seizure activity has been reported to occur in patients following hemodialysis [36].

This study suggests that the pharmacokinetics of parent ifosfamide may not be substantially altered in patients with renal failure, as has been observed with cyclophosphamide [16–18]. This patient did not experience untoward hematologic toxicities and yet significant neurologic toxicities were observed. The alteration in the pharmacokinetics of ifosfamide metabolites with possible accumulation of toxic compounds cannot be excluded. It appears that hemodialysis is at least partially effective in removing of ifosfamide and some of its metabolites. Hemodialysis may be useful in treating severe ifosfamide neurotoxicity in patients with normal or impaired renal function. The limited data presented here make it impossible to provide recommendations regarding dose adjustment of ifosfamide in patients with renal failure.

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Appendix

The amount of ifosfamide removed by the hemodialyzer at a given time "t" is the difference in the amount flowing into the dialyzer and the amount flowing out. This can be expressed as follows:

$$\frac{d(\text{Amount}(t))}{dt} = BFR_i \times C_i(t) - BFR_o \times C_o(t) \qquad \text{Eq. 1}$$

where BFR_i and BFR_o represent the blood flow rates into and out of the dialyzer respectively, and C_i (t)and C_o (t)represent the blood concentrations of ifosfamide at the dialyzer intake and outflow at time "t", respectively. Because the ultrafiltration rate was negligible compared with the blood flow rate, $BFR_i = BFR_o$.

The total amount of ifosfamide removed would then be determined by integrating the amount removed at time "t" from the beginning of dialysis (t = 0) to the end of dialysis (t = T). This can be expressed as follows:

$$\text{Total removed} = \int_{t=0}^{t=T} BFR \times (C_i(t) - C_o(t))\, dt \qquad \text{Eq. 2}$$

Because the blood flow rate was constant, Eq. 2 can be rewritten as follows:

$$\text{Total removed} = BFR \int_{t=0}^{t=T} (C_i(t) - C_o(t))\, dt \qquad \text{Eq. 3}$$

When the predialyzer (C_i (t)) and postdialyzer (C_o (t)) concentrations from the in vitro dialysis model were plotted against time, they were fit very well with a single exponential equation. Thus, the equation now takes the form:

$$\text{Total removed} = BFR \int_{t=0}^{t=T} (a_i e^{-kl \times t} - a_o e^{-k2 \times t})\, dt \qquad \text{Eq. 4}$$

where $C_i(t) = a_i e^{-k1 \times t}$ and $C_o(t) = a_o e^{-k2 \times t}$.The rate constants, k1 and k2, were determined from the in vitro dialysis. This integral can be thought of as the "area between the two curves" multiplied by the BFR. This computation for the amount removed gave a result that was very close to the actual amount of ifosfamide removed which was calculated as:

$$\text{Actual amount removed} = \text{volume} \times (C(t=0) - C(t=T)) \qquad \text{Eq. 5}$$

where "volume" is the volume of the container.

This approach was applied to the pre- and postdialysis blood concentrations of ifosfamide in the patient to estimate the amount of drug removed with each dialysis session.

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