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Chronopharmacokinetics Variation of Doxorubicin in a Pediatric Patient with Osteosarcoma Triggers Adverse Effects

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1. Abstract

1.1. Aims: This is a case report that exemplifies the chronopharmacokinetic differences of Doxorubicin (Dox), depending on time of administration of the drug because of biological rhythms, and its repercussions on adverse reactions.

1.2. Case Report: A 9-year-old female patient with Osteosarcoma (OS), with two pharmacokinetic studies of DOX conducted, in two different days, received two 48 hours-long intravenous infusions of this drug. There was a two-week period in-between, maintaining the same length of administration, and only differing by the time of day the first starting at 16 hours and the second at 2 hours am.

1.3. Results: There were no adverse effects in the patient at the end of the first infusion. However, after 8 hours of completing the second infusion with DOX, the patient presented a state of shock, low blood pressure and symptoms including extreme fatigue, disorientation, nausea, diarrhea, and general pain. The pharmacokinetic profiles obtained at the end of each infusion revealed that during the second infusion, the patient had a greater area under the curve (1.626 ng/h /ml vs 1.391 ng /h/ ml), with a much shorter half-life time (2.19 hours vs. 6.63 hours t1/2).

1.4. Conclusions: Our report suggests that these adverse effects may be related to the time of drug was administrated by effects of biological rhythms.

2. Introduction

OS is the most common type of primary malignant bone tumor, and is defined by the presence of malignant mesenchymal cells that produce osteoid or immature tissue. The most frequent type of OS is the high-grade central OS, typically presenting in the first or second decade of life, during the period of accelerated growth in adolescence, suggesting that bone growth and pubertal hormones are important in the etiology of the disease [1-2]. Unfortunately, clinical outcomes and therapeutic advances for osteosarcoma treatment have not substantially improved over the last 35 years. This lagging in therapeutic advances may be explained by the genetic, epigenetic and biological complexities of this rare tumor. Approved in 1967 in Europe and in 1974 in the United States of America, Doxorubicin (DOX) was introduced as a treatment for various neoplasms, including OS [3-4]. Since then, chemotherapy with DOX has been an essential part of the treatment protocol of OS patients [5-6]. However, it is known that it can also generate various adverse effects and even some types of toxicity [7-8]. The therapeutic window for DOX dosing is narrow, so a better understanding of the pharmacokinetics in children with OS is cru-

cial [9]. The optimal program regarding tumor cytotoxicity and dose-limiting side effects, rate, time of infusion, myelo-suppression, or cardiotoxicity has never been prospectively investigated in a randomized controlled trial [10]. Studies of all antineoplastic drugs used in cancer treatment in children are needed. Methotrexate appears to be the most studied agent. In this last, individualized and adaptive dosing has been shown to correlate with improvement in the response to therapy without increased toxicity in children with ALL and osteosarcoma. [11] In other common antineoplastic drugs, pharmacokinetics has been reported to correlate with toxicity, including DOX. There are several factors that may cause toxicity in oncological patients, among which the most important is related to chronopharmacokinetics or time of administration of the drug. [12-14] For this reason, research is needed to clarify the influence of biological rhythms on DOX biotransformation from its chronopharmacokinetics that have not been reported, as well as its relationship with the time of administration.

3. Methods

For the purposes of this study and to know the pharmacokinetics of Dox, an analytical method by High Performance Liquid Chromatography (HPLC) for the concentrations of Dox in blood was developed and validated, which is being prepared for publication with which the pharmacokinetic profile and the Area Under Curve (AUC), the Clarance (Cl), the volume of distribution and the time elimination half-life were obtained.

4. Case Report

A 9-year-old female patient with no significant medical or family history, suffered a sports trauma in August 2019 in her right shoulder. She had a fracture in the head of the right humerus with no further complications. Because of the lack of progress during the rehabilitation and after several weeks, a routine evaluation was done. The x rays showed an increase density in the adjacent tissue, with an image of the Cold-man triangle in the lateral and medial part of the same, also small disseminated calcifications. With suspicion of OS, a biopsy of the bone and soft tissues was taken, and a CT scans showed involvement at medullary level up to the cartilage of the distal growth of the humerus, thus determining the diagnosis of OS of the proximal third. As part of the chemotherapy protocol, 50 mg of DOX was administered intravenously in a 24-hour infusion on December 17 and 18 in 2019, over 48 hours. In addition, as a cardioprotective agent, 500 mg IV of cardioxane was administered in a one-hour infusion before the DOX. The complementary treatments administered are shown in Table 1. The DOX infusion began at 4 p.m. on December 17, 2019, post-infusion, followed by routine monitoring. At the end of the infusion, there were no adverse effects or discomfort referred by the patient. Two weeks later; on January 6, 2020, a second dose of DOX was administered, at the same concentration as the previous one. In this occasion, the infusion began at 2 am. Table 2 shows the rest of the drugs administered. Knowing that DOX is an antineoplastic agent that can cause toxicity [13], a pharmacokinetic study along with its routine follow-up are shown in Table 3 and the concentrations obtained from both studies are shown in Table 4. At 8 hours after ending the second infusion with DOX, the patient developed low blood pressure, disorientation, nausea, diarrhea, extreme fatigue and malaise. Complete blood count and a comprehensive metabolic panel were obtained (Table 5, A and B). After plotting the concentrations of both infusions (Figure 1, A-C), a larger are under the curve (1.626 ng*h/ml vs 1.391 ng*h/ml), with a shorter half-life (2.19 hrs t1/2 vs 6.63 hrs t1/2) was found. (The pharmacokinetic values obtained are shown in Table 6).

Table 1: Medications administered together with the first dose of Dox.

Medicine	Route of administration	Dose
Ondansetron	I.V.	8 mg c/8 hours
Apprepitant	I.V.	1 jar DU
Mannitol 20%	I.V.	210 mL / 30 minutes
Cisplatin	I.V.	120 mg / 2 hours
Calcium	P.O.	600mg c/12 hours
Magnesium	P.O.	300mg c/12 hours
Dexamethasone	I.V.	8 mg c/6 hours * 3

Intravenous (I.V.); Oral administration (Per os) (P.O.); mL: Milliliters; mg: milligram.

Table 2: Medications administered together with the second dose of Dox.

Medicine	Route of administration	Dose
Sodium bicarbonate	I.V.	40 mL
KCL	I.V.	20 meq c/6 hours
Ondansetron	I.V.	8 mg c/8 hours
Mannitol 20%	I.V.	210 mL half load
Apprepitant	I.V.	1 jar DU
Mannitol 20%	I.V.	210 mL / 30 minutes
Cisplatin	I.V.	120 mg / 2 hours
Calcium	P.O.	600 mg c/12 hours
Magnesium	P.O.	300 mg c/12 hours
Dexamethasone	I.V.	8 mg c/6 hours * 3

Intravenous (I.V.); Oral administration (Per os) (P.O.); mL: Milliliters; mg: milligram.

Table 3: Sampling times for the two pharmacokinetic studies performed on the patient.

Time / hour	Number of sample	Infusion 1	Infusion 2
Before infusión			
0	1	X	X
During the infusion			
1	2	X	X
24	3	X	X
48	4	X	X
After infusion			
1	5	X	X
2	6	X	X
6	7	X	X
8	8	X	X
15	9	X	X
20	10		

Table 4: Concentrations recorded in each sample from the two different pharmacokinetic studies performed on the patient.

Number of Sample	Concentrations during infusion 1(ng/mL)	Concentrations during infusion 2 (ng/mL)
1	0	0
2	189	201
3	279	293
4	197.5	284.2
5	108.2	295.6
6	97.5	296
7	81.7	122
8	67.5	80.5
9	25.3	44.3
10	0	0

ng: nanograms; mL: Milliliters.

Table 5: Values of partial hematic biometry (A) and blood chemistry and serum electrolytes (B).

A	HEMATIC BIOMETRY		
PARAMETERS	**RESULTS**	**REFERENCE VALUES**	
		Male	Female
LEUKOCYTES	46.3	4.5	11
NEUTROPHILES	96.4	39.3	73.7
LYMPHOCYTES	2.83	20-40	
MONOCYTES	0.66	4.40-12.7	
EOSINOPHILS	0.01	0.6-7.3	
BASOPHILES	0.08	0.0-1.7	
ERYTHROCYTES	4.4	5.0-6.3	4.0-5.7
HEMOGLOBIN	11.9	14-16	12-14
HEMATOCRITO	34.7	43.4-49.6	37.1-43.4
MGV	79	83-98	78-103
MGHC	34.3	32-34.4	31.8-35.4
RDW	11.8	11.5-14.5	
PLATELETS	168	155000-366000	

B	BLOOD CHEMISTRY AND SERIC ELECTROLYTS		
PARAMETERS	**RESULTS**	**REFERENCE VALUES**	**UNITS**
Glucose	109	70-100	Mg/dL
Urea	34	20-Jul	Mg/dL
Creatinine	0.7	15-43	Mg/dL
Sodium	134	0.7-1.5	Mmol/L
Potassium	2.5	135.0-5.5	Mmol/L
Chloride	100	96-106	Mmol/L

MGV: Mean globular volume; C. Hb. G. M: Mean Globular Hemoglobin Concentration; RDW: Red cell distribution width; Mg: Milligrams; dL: Deciliters; Mmol: Millimolar; L: Liters.

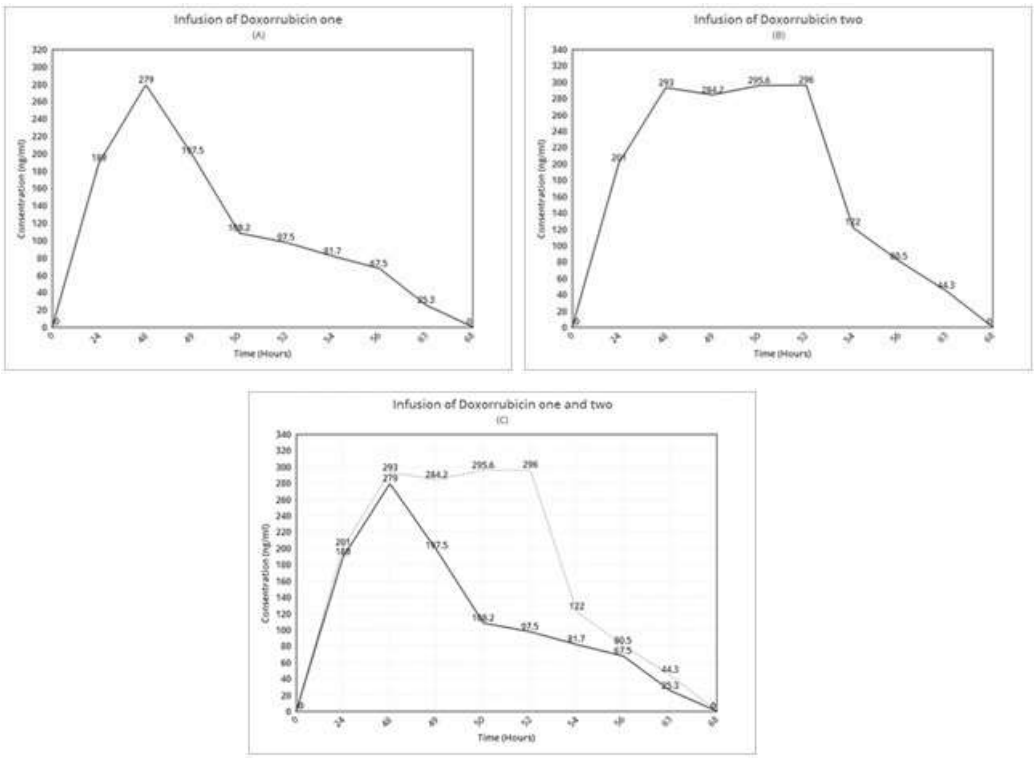

Figure 1: Comparison between the two different Dox pharmacokinetic curves, performed in the patient with osteosarcoma. Infusion 1 (A), Infusion 2 (B) and Infusion 1 and 2 (C).

Table 6: Pharmacokinetic values.

Infusion number	Elimination rate constant(h-1)	Volumen of distribution (L)	Clearance (L/h)	Half- time (h)	Area down the curve (ng*h/mL)
1	0.1	834.04	87.17	6.63	1.391
2	0.32	179.52	56.75	2.19	1.626

ng: nanogram h: hours; L: Liters mL: milliliter

5. Discussion

The understanding of the chronopharmacology and pharmacokinetics of doxorubicin in children is limited, and evidence is conflicting. The aim of this case report is to review the correlation in the clearance of doxorubicin while factoring-in the time of the drug administration. Review of different variables indicate that greater area under the curve 1.626 ng*h/ml vs 1.391 ng*h/ml) is associated with the presence of adverse effects. These results seem to be very significant since Krischke et al., in 2016 [15] that included one hundred and one patients (children with cancer) were recruited and the objective was to measure DOX elimination. The results showed that troponin levels increased with increasing DOX exposure, a limited correlation between its blood levels and DOX pharmacokinetics could be observed. The age dependence of doxorubicin clearance, and children under 3 years had a statistically significant lower clearance (21.1 ± 5.8 l/h/m2) than older children (26.6 ± 6.7 l /h/m2) (p=0.0004). On the other hand, Canal et al. [12] studied the chronopharmacokinetics of DOX in 18 patients suffering from breast cancer. These patients received combined chemotherapy, including DOX (50 mg/m2 in IV bolus), administered at two different times (9 am to 9 pm). The two randomized courses of the protocol were administered to each patient at a four weeks' interval. As a result, DOX total body clearance decreased significantly when the drug was administered at 9 p.m., resulting in a longer half-life elimination and increased Area Under Curve (AUC). This case shows that when DOX was administered at 2 am, there was a longer and higher DOX concentration than when it was administered at 4 pm. The toxicity of drugs considering the chronopharmacological aspect, is poorly studied. In 2012, Erkekoglu and Baydar mentioned that is crucial to study the chronobiology and the Chronopharmacokinetics of drugs in toxicological aspects. For decades, we know that biological rhythms and drug metabolism are also affected by circadian cycle and chronopharmacology was recognized by scientists in the early 1970s [16-17].

6. Conclusions

The results show that longer time it took for DOX to start being removed had adverse effects on the patient. This may be related to the time of drug administration. The results show a delay in the DOX elimination during the second infusion; whereas in the afternoon infusion the elimination curve starts 48 hours after the infusion was started.

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