Pharmacokinetic evaluation of anticancer drugs in Hodgkin's lymphoma patients after their simultaneous administration

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Abstract: A pharmacokinetic study of anticancer drugs was carried out in 18 Hodgkin's lymphoma male patients. The anticancer drugs were administered to the patient by a standard procedure and a validated HPLC method was used for plasma concentration determination. Maximum plasma concentration (C_{max}) of Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) were 7.71, 4.32, 7.95 and 6.51µg/ml respectively. Adriamycin and Dacarbazine exhibited longer T_{max} compared to Bleomycin and Vinblastine. Area under the curve values of ABVD were 118.30, 82.11, 245.54 and 86.62µg/ml*h. The elimination rate constant of Dacarbazine was highest. Vinblastine exhibited highest half-life and mean residence time. Clearances of ABVD were 346.69, 2499.44, 45.90 and 5800.05ml/h. The apparent volume of distribution was highest for Dacarbazine and lowest for Vinblastine. The pharmacokinetic parameters can be utilized for monitoring of plasma concentrations, therapeutic drug monitoring and dosage adjustments to optimize anticancer efficacy in patients of Hodgkin's lymphoma.

Keywords: Pharmacokinetic Parameters, Adriamycin, Bleomycin, Vinblastine, Dacarbazine, Hodgkin's Lymphoma.

INTRODUCTION

Extramedullary tumors arising primarily in the lymph nodes or other sites called Lymphomas. Lymphomas are divided into two types; Hodgkin's Lymphomas and Non-Hodgkin's Lymphomas. In Hodgkin's lymphoma there is an orderly spread of disease from one lymph node group to another and is characterized by multinucleated Red-Strenberg cells. The ABVD chemotherapy - stands for the four drugs adriamycin an anthracycline (Rodney *et al*., 2003), bleomycin a glycopeptides (Mohamed *et al.*, 2004; Usman *et al*., 2010), vinblastine an alkaloid (Creasey *et al.,* 1975) and dacarbazine an alkylating agents (Stephanie *et al*., 2001). This combination is the standard treatment of Hodgkin's lymphoma in US. It was developed in Italy in the 1970s, it takes 6-8 months and longer treatments may be required.

The successful drug therapy is highly dependent on the selection of the drugs and their dosage regimen. Drug product selection is based on pharmacokinetics of the drug and characteristics the patient. A correctly designed dosage regimen helps to attain required drug concentration at site of action to produce an optimal therapeutic response (Shargel *et al.*, 2005).

To achieve maximum therapeutic benefits with minimum side effects evaluation and monitoring of the patient is required. The variation in pharmacokinetics and pharmacodynamics of makes the dosage regimens plan of anticancer drugs more complicated. Therefore, application of pharmacokinetics parameters is important in designing the dosage regimens plan of anticancer drugs. The current study was aimed to evaluate pharmacokinetics of four anticancer drugs Adriamycin, Bleomycin, Vinblastine and Dacarbazine. A comparative pharmacokinetic evaluation of anticnacer drugs after their simultaneous administration to treat lymphoma has not been reported previously. This type of study is extremely required and will be helpful in dosage regimen design and its individualization where the combined therapy will be given to Hodgkin's lymphoma patients.

MATERIALS AND METHODS

Disodium hydrogen phosphate, Acetonitrile, Phosphoric acid and Trichloroacetic acid were purchased from Merck, Germany whereas Triethylamine was purchased from Fluka, Switzerland. The reference standards of Adriamycin (India), Bleomycin (China), Vinblastine (China) and Dacarbazine (China) were obtained from Pharmedic Laboratories private limited Pakistan.

Administration of dugs

The elements of protocols of the current study were approved by Pharmacy Research Ethics Committee, the Islamia University of Bahawalpur. The anticancer drugs Adriamycin, Bleomycin, Vinblastine and Dacarbazine were administered to 18 Hodgkin's lymphoma cancer patients of 12-55 years old by the Bahawalpur Institute of Nuclear Medicine & Oncology (BINO) staff through a standard procedure i.e. Bleomycin and Vinblastine were

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administered through IV bolus injections separately whereas Adriamycin and Dacarbazine were administered in a saline or dextrose or Ringer lactate infusion depending on the condition of the patient.

Sample collection

A 3ml blood sample was collected before drug administration and then at 5, 10, 20, 30 minutes and 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 8.0, 12.0, 18.0, 24.0, 36.0, 48.0, 72.0 and 96.0 hours. Blood samples were centrifuged at 5000 rpm for 10 minutes and recovered plasma was frozen at -80°C in the ultra low refrigerator until analyzed.

Method for drug analysis

Agilent 1200 series chromatograph consisted of isocratic pump with UV-detector, Chromatographic separation was performed on ODS hypersil C_{18} stainless steel analytical column, 5µm pore size, 4.6mm×250mm (Thermo Electron Corporation, UK). The flow rate was 0.75 ml/minutes at wave-length of 230nm. The mobile phase consisted of 300ml acetonitrile and 700ml 0.5M disodium hydrogen phosphate containing 0.5ml triethylamine and pH of the mobiles phase was maintained at 3.7 with 2M phosphoric acid (Zubair *et al*., 2013).

Plasma spiking and extraction procedure

The plasma was spiked with reference standards containing 0.098, 25 and 50µg/ml of each of Adriamycin, Bleomycin, Vinblastine and Dacarbazine. The compounds were recovered by precipitating the plasma with 20µl trichloroacetic acid and centrifuging at 5000rpm for 10 minutes and then injecting the supernatant into the chromatograph after membrane filtration. Pharmacokinetic analysis was done by Kinetica software version 4.4.1.

RESULTS

The values of pharmacokinetic parameters i.e, Maximum plasma concentration, Time to reach C_{max}, Area under the curve, Elimination rate constants, Half-life Mean residence time, Clearance and Volume of distribution of Adriamycin, Bleomycin, Vinblastine and Dacarbazine are presented in table 1. The plasma level time curve of these anticancer drugs in Hodgkin's Lymphoma patients is shown in fig 1.

DISCUSSION

Pharmacokinetic parameters of anticancer drugs

In a previous study on Sulphur-crested cockatoos the AUC was 950ng. h/ml and C_{max} was 4.037µg/ml (Gilbert *et al*., 2004). The discrepancy in values may be due to species differences as well as conditions and established protocols designed for these studies. $T_{1/2}$ and Cl_T of Adriamycin was consistent with Raymond *et al*. (1983) and Frost *et al.* (2002). For Bleomycin, the pharmacokinetic parameters (AUC, C_{max},T_{max}, $T_{1/2}$, MRT and Ke) were almost consistent with the previous study done by Alberts *et al.* (1979). The AUC, C_{max}, T_{max}, $T_{1/2}$, MRT and Ke Vinblastine were similar to that of Ratain *et al.* (1987). The values of pharmacokinetic parameters of Decarbazine were consistent with the literature (Breithaupt *et al.*, 1982).

Inter-comparison of parameters

Once plasma concentration-time data have been fitted, most of the pharmacokinetic parameters can be generated (Gibaldi and Donald, 2007).

Maximum plasma concentration (C_{max}) of Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) were 7.71, 4.32, 7.95 and 6.51µg/ml respectively (fig. 1). C_{max} represented the maximum concentration of anticancer drugs in plasma or serum. Plasma drug concentrations are affected by the rate of administration, volume of distribution and clearance of drugs. Highest C_{max} value of vinblastine was because of its rapid availability in plasma after IV injection. Because of slow infusion rate Bleomycin and Dacarbazine were eliminated from body beside their availability in plasma (Breithaupt *et al.*, 1982). It resulted in their low C_{max} compared to vinblastine.

Time to reach maximum plasma concentration (T_{max}) defines the time when maximum drug is present in plasma. T_{max} values of ABVD were 0.66, 0.10, 0.08 and 1.22 hours respectively. Shorter T_{max} of Bleomycin and Vinblastine was due their IV bolus injection directly into the patient blood stream. Whereas Adriamycin and Dacarbazine exhibited longer T_{max} because of their slow infusion into blood stream.

Area under the curve ($AUC_{0-\infty}$) of ABVD were 118.30, 82.11, 245.54 and 86.62µg/ml*h. Rapid excretion from the body and lack of absorption phase resulted in lowest AUC of Bleomycin. Contrary to this Vinblastine showed high AUC due slow excretion and high plasma concentration.

Elimination rate constants (K_e) of ABVD were 0.04, 0.05, 0.02 and 0.12h^{-1} respectively. High K_e value of Dacarbazine represented its rapid removal from the body and its AUC was low for the same reason. Adriamycin had comparatively slow excretion process and can maintain their concentration for longer period of time.

The time required to reduce the plasma concentration to one half its initial value is called half-life ($t_{1/2}$). Half-life of a drug is determined by its clearance and the volume of distribution. Half-life of ABVD were 22.81, 4.15, 35.06 and 6.80 hours. Vinblastine has highest half-life among all that's because of its slow excretion (Kramer *et al.*, 1978; Dorr, 1992). The highest half-life of Vinblastine is

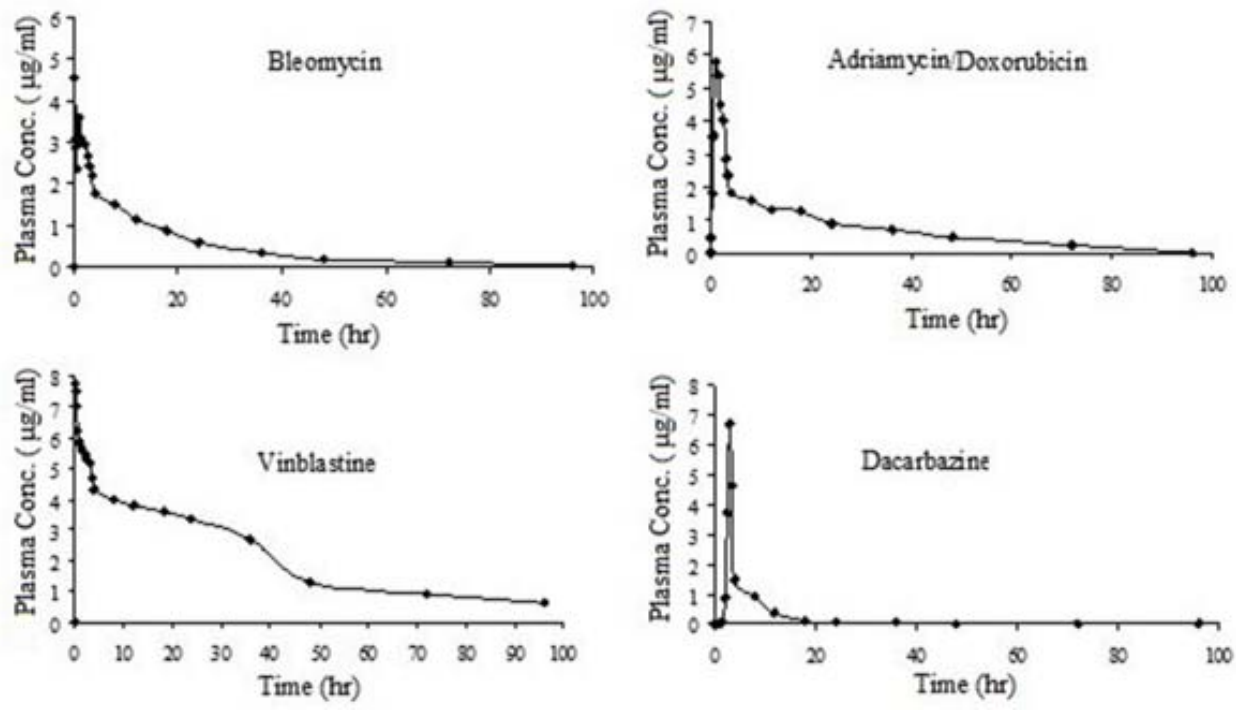

Fig. 1: Plasma level curve of anticancer drugs in Hodgkin's lymphoma patients during the course of treatment

Table 1: Bioavailability and pharmacokinetic parameters (mean±SEM) of anticancer drugs in Hodgkin's lymphoma patients

Drug	C_{max} (µg/ml)	T_{max} (h)	$AUC_{0-\infty}$ (µg/ml*h)	$K_e(h^{-1})$	$T_{1/2}$ (h)	MRT (h)	Clearance (ml/h)	Vd (L/Kg)
Adriamycin	7.71 ±2.24	0.66 ±0.25	118.30 ±68.37	0.04 ±0.02	22.81 ±9.86	29.11 ±8.19	346.69 ±113.86	11.31 ±6.84
Bleomycin	4.32 ±0.90	0.10 ±0.06	82.11 ±49.49	0.05 ±0.01	4.15 ±2.16	21.15 ±3.53	2499.44 ±2794.94	16.77 ±5.31
Vinblastine	7.95 ±0.72	0.08 ±0.00	245.54 ±89.39	0.02 ±0.01	35.06 ±11.27	48.75 ±15.12	45.90 ±23.89	2.03 ±0.67
Dacarbazine	6.51 ±2.81	1.22 ±0.65	86.62 ±33.40	0.12 ±0.04	6.80 ±3.18	9.66 ±4.23	5800.05 ±2282.24	51.64 ±21.48

also responsible for its maximum MRT in plasma (48.75 hours).

Clearance does not represent the amount of drug being removed rather it indicates the volume of plasma in the vascular compartment cleared of drug per unit time by the processes of metabolism and excretion. It is the most important pharmacokinetic parameter because it determines the maintenance dose (Larry, 2008). Clearances of ABVD were 346.69, 2499.44, 45.90 and 5800.05ml/h. Dacarbazine showed maximum clearance rate because of its highest elimination rate constant and multiple excretory mechnisms i.e., tubular secretion along with hepatobiliary and pulmonary excretion (Chabner and Longo, 2006). High clearance rate also resulted in its lowest MRT in the body.

Slow clearance of Vinblastine may be due to its bilary excretion (Chabner and Longo, 2006). The volume of distribution is also an important pharmacokinetic parameter. Although it does not have an exact physiologic significance, but it can indicate the extent of drug distribution, so often referred to as the apparent volume of distribution (V_d). It aids in determination of dosage requirements (Malcolm and Tozer, 1995). Apparent volume of distribution of ABVD were 11.31, 16.77, 2.03 and 51.64L/Kg respectively. Dacarbazine has highest V_d indicating the requirement of larger doses to achieve a desired target concentration at receptor site. Where as Vinblastine requires administration of minimum dose to accomplish sufficient concentration for optimal therapeutic response.

CONCLUSION

After simultaneous administration maximum plasma concentration of anticancer drugs were within therapeutic range so can be used in standard doses to treat Hodgkin's lymphoma. Due to highest cleance and elimination rate constant, Deacabazibe was rapidly excreted so it may

require frequent doses to maintain it's therapeutic level in plasma. On the other hand long half-life and MRT of vinblastine enabled its prolonged availability in patient's body. The pharmacokinetic parameters may be helpful for local patients with Hodgkin's lymphoma by making treatment more effective.

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