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 (Cmax) of Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) were 7.71, 4.32, 7.95 and 6.51µg/ml respectively. Adriamycin and Dacarbazine exhibited longer Tmax 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. Vinblas tine 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 anticancer 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 drugs

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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...were 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 C18 stainless steel analytical column, 5µm pore size, 4.6mm x 250mm (Thermo Electron Corporation, UK). The flow rate was 0.75 ml/minute 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 Kineta 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 Vinblaste were similar to that of Ratain et al. (1987). The values of pharmacokinetic parameters of Dacarbazine 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 vinblaste 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 vinblaste.

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 Vinblaste 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) 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 Vinblaste 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. Vinblaste has highest half-life among all that’s because of its slow excretion (Kramer et al., 1978; Dorr, 1992). The highest half-life of Vinblaste is...
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 5800.05 ml/h. Dacarbazine showed maximum clearance rate because of its highest elimination rate constant and multiple excretory mechanisms 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 biliary 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 51.64 L/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 clearance and elimination rate constant, Deacabazibe was rapidly excreted so it may
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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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REFERENCES


