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Effect of Ciprofloxacin on the Plasma Concentration of Doxorubicin, Following Acute and Chronic Dose Protocol in Sprague Dawley Rats

Andleeb Shahzadi and Zeliha Yazici
Department of Medical Pharmacology, Cerrahpasa Faculty of Medicine,
Istanbul University, Turkey

Abstract: The objectives of the present study were to evaluate an interaction at plasma level between doxorubicin (Doxo) and ciprofloxacin (Cipro) and to determine schedule dependent (acute-chronic) effect of Doxo alone and in combination with Cipro on the plasma concentration ofmale adult Sprague Dawley rats. In the chronic protocol, rats were randomized to receive intra-peritoneal (i.p.) injections of 1 or 2.5 mg kg^{-1} (twice a week) of Doxo alone and in combination with Cipro (20 mg kg^{-1} daily) for the duration of 3 weeks along with a placebo control. For acute schedule, rats were subjected to receive Doxo alone (6 or 15 mg kg^{-1}) or in combination with Cipro (20 mg kg^{-1}) as a single i.p., injection and placebo treatment with saline (control). The plasma levels of Doxo were measured by using Enzyme-Linked Immuno Sorbent Assay (ELISA) technique. The plasma concentration of Doxo after the treatment with Doxo alone or in combination with Cipro (20 mg kg^{-1}) significantly increased than that of control ($p<0.0001$). Cipro (20 mg kg^{-1}) significantly increased the plasma concentration of Doxo following chronic and acute protocols (1 or 6 mg kg^{-1}) by 26 and 23%, respectively. The plasma concentration of Doxo in acute (15 mg kg^{-1}) and chronic (2.5 mg kg^{-1}) group was significantly increased by 16.4 and 14.3%, respectively. Whereas, acute or chronic dose protocol did not show any significant differences. The increase in plasma concentration with Doxo +Cipro can be subjected to the inhibition of CYP3A4 and CYP1A2 isoenzyme by Cipro which is thought to be responsible for metabolism of Doxo. The increase in plasma concentration can lead to unforeseen toxicities. The present study also stresses on the pharmacokinetic investigation in human and the population where the drug is to be employed clinically because of polymorphism and inter-individual variation.

Key words: Ciprofloxacin, CYP450 enzymes, doxorubicin, drug-drug interaction

INTRODUCTION

Advances in the field of science from the last decade have improved our knowledge of understanding the pharmacology (pharmacokinetics and pharmacodynamics) of anticancer drugs. Anticancer drugs have narrow therapeutic index and high inter-individual pharmacokinetic variation required optimal dosing. Therefore, understanding the principles of pharmacokinetics has high clinical relevance.

Chemotherapy is associated with intensive dose regimens that lead to prolonged neutropenia and increased risk of bacterial infections. Neutropenia, one of the most serious hematologic toxicity, is related with the risk of life-threatening infections that leads to dose reduction of anticancer drugs which ultimately delays the treatment effects (Crawford *et al*., 2004). During the last decade, fluoroquinolones have been increasingly used to treat chemotherapy related neutropenia (Engels *et al*., 1999). Meta-analysis of 1,408 neutropenic patients showed a significant reduction in the incidence of Gram-negative bacterial infections, total infections and episodes with fever following the treatment of fluoroquinolones (Engels *et al*., 1999). The prophylactic use of antibiotics like ciprofloxacin and roxithromycin against two placebos along with cyclophosphamide, doxorubicin and etoposide reduced the incidence of Febrile Neutropenia (FN), exposure to different kind of infections, use of other antibiotics, number of hospitalizations due to FN was also decreased approximately 50% and less deaths was reported due to infection in patients suffering with small-cell lung cancer (Tjan-Heijnen *et al*., 2001).

Now a days, chemotherapy regimens used in clinical practice are empiric drug combinations designed in the absence of in vitro experimental data (Fan *et al*., 1998; Zoli *et al*., 2001) often these drug combinations can lead to drug-drug interactions. Drug interactions are one of the leading causes of morbidity and mortality in health care (Shahzadi *et al*., 2011). Knowledge regarding drug

Corresponding Author: Andleeb Shahzadi, Department of Medical Pharmacology, Cerrahpasa Faculty of Medicine, Istanbul University, Turkey Tel: 0090-5545083451 Fax: 0090-2124143082

interaction is very important for health care professionals, regulatory authorities and pharmaceutical agencies (Badyal and Garg, 2000). Drug interactions can result into decreased or increased efficacy or toxicity of drug which can lead to unseen adverse effects (Shahzadi *et al*., 2011). Most prevalent and extensively reported are the pharmacokinetic interactions most of them are due to the change in CYP450 enzyme metabolism. Clinically significant drug interactions do occur in cancer chemotherapy and it is likely that important interactions have not been recognized. Little information is available about the pharmacokinetic interactions of anticancer drugs in humans (Kivisto *et al*., 1995).

Ciprofloxacin (Cipro) belongs to fluoroquinolones, is a wide spectrum antibiotic active against wide range of gram positive and negative bacteria (Wolfson and Hooper, 1989). Ciprofloxacin is also widely prescribed during chemotherapy whether to treat neutropenia or as a supporting therapy to treat bladder cancer, colorectal cancer and prostate cancer (Aranha *et al*., 2003; Gurtowska *et al*., 2010; Herold *et al*., 2002). Ciprofloxacin mainly inhibitor of metabolizing CYP1A2 isoenzyme (Jerling *et al*., 1994) and reversibly metabolized by CYP3A4 isoenzyme (Von Moltke *et al*., 1996).

Doxorubicin (Doxo), an antineoplastic agent, is extensively used in clinical practice to treat solid and hematological malignancies (Lebrecht and Walker, 2007). Doxo is widely used in clinical practice in combination with certain other drugs to increase its efficacy or to treat other related toxicities. While reviewing the pharmacokinetic profile of Doxo it has been found that it is metabolized by CYP3A4 isoenzyme.

Literature showed Doxo and Cipro are frequently prescribed in clinical practice and interaction may result without recognition. As both these drugs flow the metabolism by (CYP3A4 and CYP1A2 isoenzymes) which can be a cause of toxicity or decreased in therapeutic efficacy. The literature regarding the influence of Cipro on the pharmacokinetics of Doxo is scanty so the present study is designed to examine the influence on the plasma concentration of Doxo alone and in combination with Cipro following acute and chronic schedule on Sprague Dawley rats. This is the first description towards the effect of Cipro on the plasma concentration Doxo this information could be a bridge between preclinical and clinical practice for physicians in making an expert opinion dealing with above mentioned group. This data will also be helpful in determining the optimal dose regimen of Doxo when given in combination with Cipro.

MATERIALS AND METHODS

The experimental protocol was approved by Experimental Animals Ethics Committee of Istanbul University Cerrahpasa Faculty of Medicine. The experimental study was performed on the plasma separated from the blood of male Sprague Dawley rats weighing between 250-300 g at the start of experiment. Animals were housed (4 animals per cage), placed in temperature-controlled (22°C) room with a 12 h light/dark cycle, they were given food and water *ad-libitum* manually.

Drugs: Ciproxin (Cipro) Flacon (400 mg; Bayer, Turkey) and Doxorubicin (Adriamycin) (Doxo) Ampoule (10 mg 5 mL^{-1}; Deva Pharmaceuticals Turkey) were purchased from a local pharmacy store.

Drugs therapy schedules: Animals (Sprague Dawley rats) were randomly divided into 10 sub-groups of 8 animals in each group to study the changes in plasma concentration induced by low and high doses of Doxo given under acute and chronic schedules alone or in combination with Cipro in Sprague Dawley rats.

Acute dose schedule: Acute group rats followed therapeutic doses (6 and 15 mg kg^{-1}) of Doxo alone administered to rats as single intra-peritoneal injection (i.p.) and in combination with ciprofloxacin (20 mg kg^{-1}; i.p.).

Chronic dose schedule: Rats in the chronic group were subjected to have multiple i.p., injections of Doxo (1 and 2.5 mg kg^{-1} twice a week for 3 weeks) alone and in combination of Cipro (20 mg kg^{-1}; i.p., daily) i.e., cumulative doses of Doxo 6 and 15 mg kg^{-1}, respectively up-to 3 weeks. Control group rats received serum physiological solution.

Animal dose protocol: Animal dose protocol is shown in Table 1.

Plasma analysis: Immediately after the completion of treatment schedule of both the chronic and acute group, blood samples of rats were collected in microtranier EDTA tubes for the extraction of plasma. Plasma was extracted by centrifugation and kept at -20°C until analysis. Plasma levels of Doxo were determined using a commercially available Enzyme-Linked Immuno Sorbent Assays (ELISA) kits (East Biopharm, China).

Double working standards having Doxo concentration 0, 75, 150, 300, 600, 1200 μmol L^{-1} were

prepared. These working standards were analyzed by ELISA concentration verses absorption and plotted on graph to construct the calibration curve (Fig. 1). The curve was linear over the range of 0 to 1200 μmol L^{-1}.

The concentration of Doxo in plasma samples of Sprague Dawley rats were determined by reading the optical density. The concentration of Doxo in plasma was obtained by using following mentioned curve (Fig. 1).

Statistical analysis: All values are presented as Mean±SEM. Statistical significance ($p<0.05$) was determined by 1-way ANOVA followed by *post-hoc* Turkey's test. In addition to this, 2 way ANOVA was used to study the interaction (Graph Pad Prism 4.0).

RESULTS

Plasma concentration of Doxo: After i.p., injection of Doxo alone following chronic (1, 2.5 mg kg^{-1} twice a week for 3 weeks, cumulative dose 6 and 15 mg kg^{-1}, respectively) and acute (6, 15 mg kg^{-1} single injection) dose protocol in Sprague Dawley rats, plasma concentration of Doxo was obtained and results are given below:

Chronic group: Pretreatment plasma levels of Doxo was 0 μmol L^{-1} in rats treated with saline solution (control group) for 3 weeks. These levels remained unchanged till the end of experiment. Significant increase ($p< 0.0001$) in Doxo plasma levels were observed in rats treated with low or high doses of Doxo alone (1 and 2.5 mg kg^{-1}; cumulative dose 6 and 15 mg kg^{-1}, respectively) and when these doses were administered in combination with Cipro (20 mg kg^{-1}) than that of control (Fig. 2). The highest concentration of Doxo was found in rats administered with Doxo + Cipro (2.5 + 20 mg kg^{-1}; cumulative Doxo dose 15 mg kg^{-1}) (Fig. 2). Whereas, the Doxo plasma concentration in rats of both treated with high dose of Doxo alone (2.5 mg kg^{-1}; cumulative Doxo dose 15 mg kg^{-1}) and in combination with Cipro (2.5 + 20 mg kg^{-1}; cumulative Doxo dose 15 mg kg^{-1}) was statistically significant (201.0 ± 7.906 vs. 229.8 ± 9.928 μmol L^{-1}, respectively) as shown in Fig. 3. Similar pattern was observed when low dose of Doxo alone (1 mg kg^{-1}; cumulative dose 6 mg kg^{-1}) was compared with Doxo+Cipro (1+20 mg kg^{-1}; cumulative Doxo dose 6 mg kg^{-1}) dose group (141.6±2.653 vs. 174.9±2.216 μmol L^{-1}, respectively) as shown in Fig. 3.

Acute group: Single i.p., injection of low or high doses of Doxo (6 and 15 mg kg^{-1}) alone and in combination with

Table 1: Animal group protocol to study the effect of Doxo alone and along with Cipro on the plasma concentration of Sprague Dawley rats

Groups	Route of administration	Cumulative dose of Doxo
Control/saline	Intra-peritoneal (i.p)	-
Doxo 1 mg kg^{-1} alone	Intra-peritoneal (i.p)	6 mg kg^{-1}
Doxo 1+Cipro 20 mg kg^{-1}	Intra-peritoneal (i.p)	6 mg kg^{-1} +-
Doxo 2.5 mg kg^{-1} alone	Intra-peritoneal (i.p)	15 mg kg^{-1}
Doxo 2.5+Cipro 20 mg kg^{-1}	Intra-peritoneal (i.p)	15 mg kg^{-1}+-

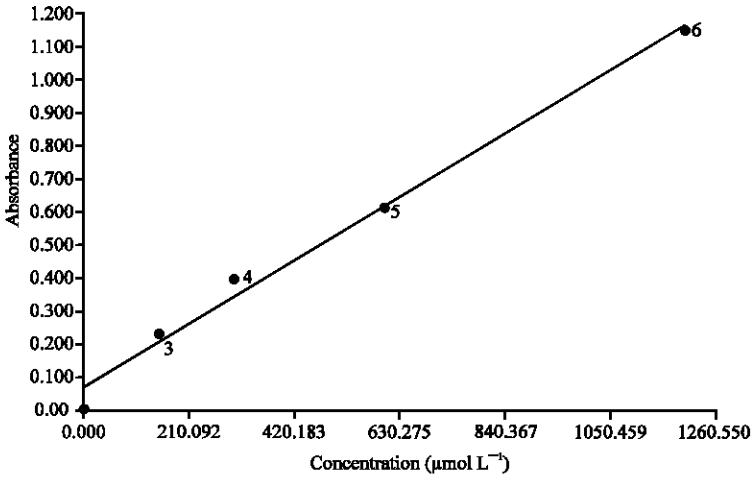

Fig. 1: Standard curve of Doxo

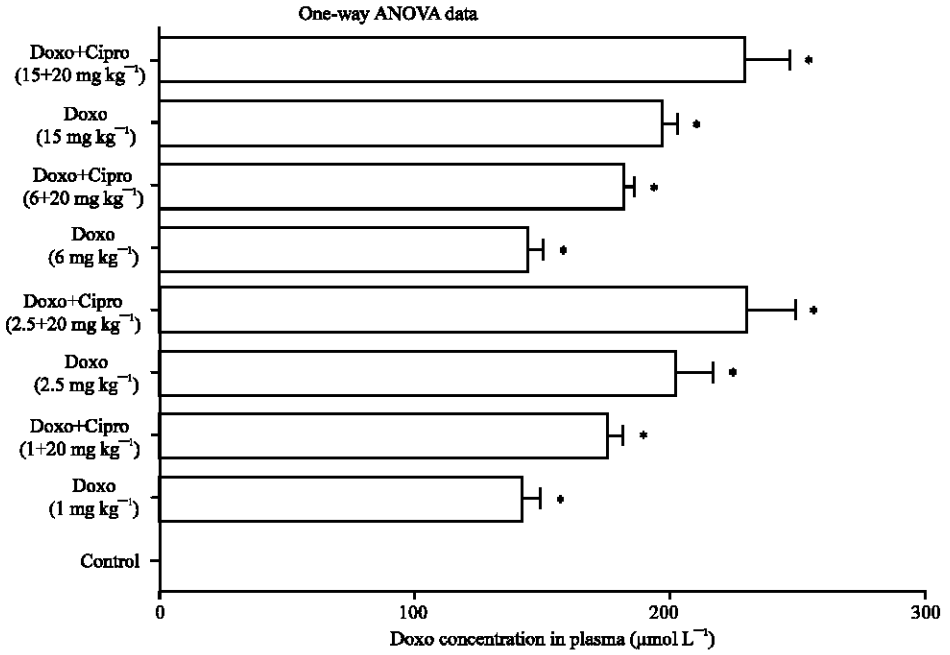

Fig. 2: Comparative mean plasma concentration of control, Doxo (1, 2.5, 6, 15 mg kg^{-1}) following its i.p., administration alone and with Cipro (20 mg kg^{-1}; i.p.) to male Sprague Dawley rats, values are the Mean±S.E, * $p<0.0001$

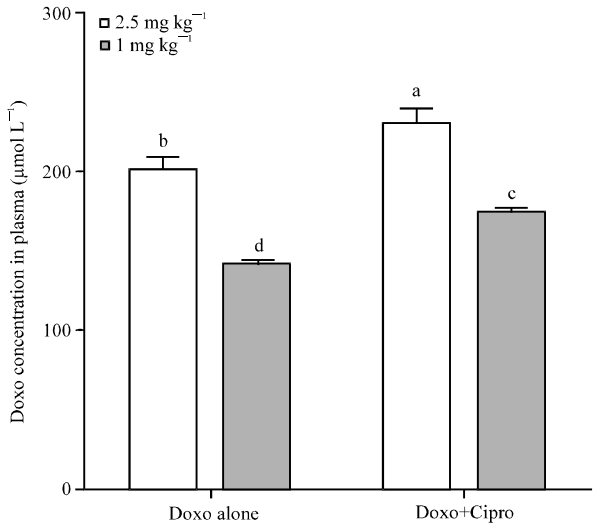

Fig. 3: Plasma concentration of rats treated chronically with multiple i.p., doses of Doxo alone (1 and 2.5 mg kg^{-1}) and in combination with Cipro (20 mg kg^{-1}; i.p.). Values are the Mean±S.E, bars having different letters are statistically significant

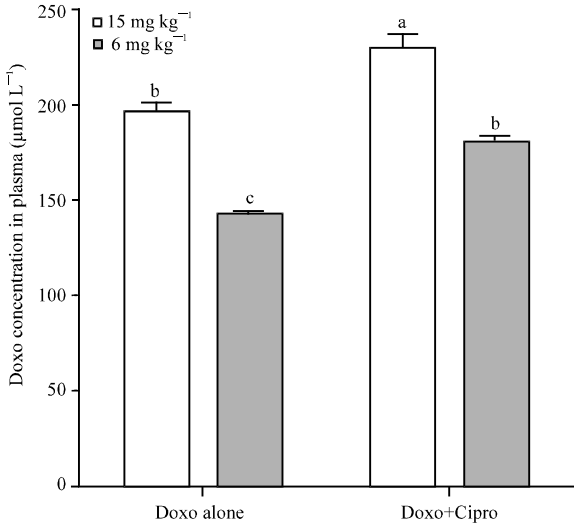

Fig. 4: Plasma concentration of rats treated with single i.p., (acute) dose of Doxo alone (6 and 15 mg kg^{-1}) and in combination with Cipro (20 mg kg^{-1}; i.p.). Values are the Mean±S.E, bars having different letters are statistically significant

Cipro (20 mg kg^{-1}) to healthy adult male rats increased the plasma Doxo concentration significantly ($p<0.0001$) than that of control (Fig. 2). Drastic increase in plasma Doxo concentration was observed in rats treated with high dose of Doxo+Cipro (15+20 mg kg^{-1}) (Fig. 4). Whereas, the Doxo plasma concentration in rats of both treated with high dose of Doxo alone (15 mg kg^{-1}) and along with Cipro (15+20 mg kg^{-1}) was statistically significant (196.0±2.989 vs. 228.2±7.846 μmol L^{-1}, respectively) as shown in Fig. 4. The low dose of Doxo

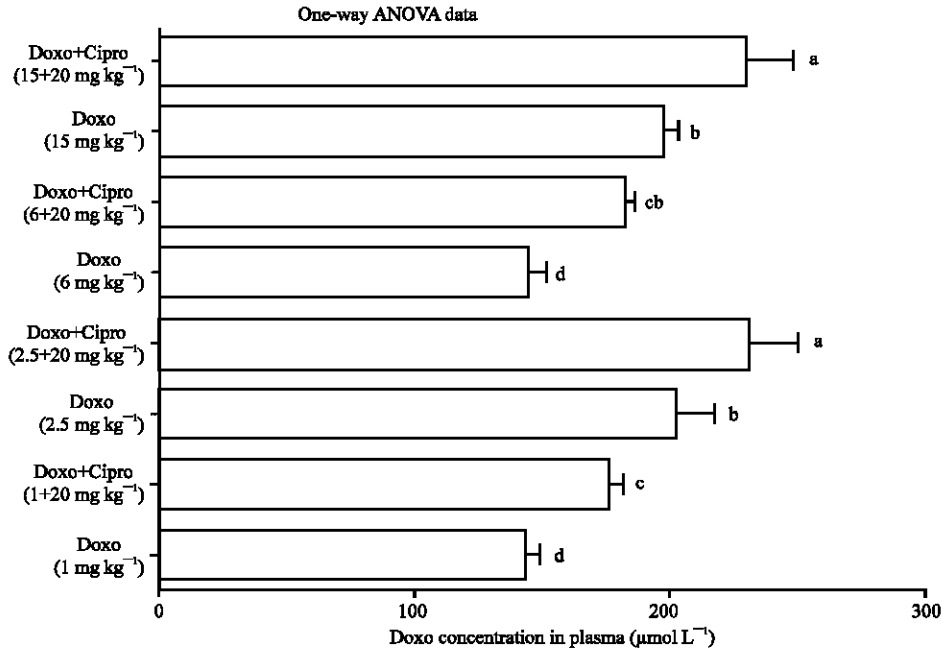

Fig. 5: Interaction between Doxo and Cipro at different doses following chronic and acute protocols in Sprague Dawley rats. Values are the Means±S.E, bars having similar letters are non-significant

alone showed a significant difference when Doxo alone (6 mg kg^{-1}) was compared with Doxo+Cipro (6+20 mg kg^{-1}) dose group (143.1±2.650 vs. 181.5±1.648 μmol L^{-1}, respectively) as shown in Fig. 4.

Interaction of acute and chronic groups: Overall comparison of acute and chronic groups following different dose protocol but with same cumulative doses (6 and 15 mg kg^{-1}) showed significant differences ($p<0.05$) but with few exceptions (Fig. 5). These exceptions includes low chronic dose of Doxo+Cipro (1+20 mg kg^{-1}; cumulative Doxo dose 6 mg kg^{-1}) vs. low acute of Doxo+Cipro (6+20 mg kg^{-1}) (174.9±2.216 vs. 181.5±1.648 μmol L^{-1}) and Doxo (1 mg kg^{-1}; cumulative Doxo dose 6 mg kg^{-1}) vs. low acute of Doxo (6 mg kg^{-1}) (141.6±2.653 vs. 143.1±2.650 μmol L^{-1}) as both these groups shares the same dose but followed different dosing protocol. Same trend was followed by high chronic dose of Doxo+Cipro (2.5 mg kg^{-1}; cumulative Doxo dose 15 mg kg^{-1}) vs. high acute of Doxo + Cipro (15 mg kg^{-1}), the rats of both these groups were administered by the same dose but with different dosing schedules (201±7.906 vs. 196±2.989 μmol L^{-1}). Interestingly, a non-significant difference was observed when chronic high dose of Doxo alone (2.5 mg kg^{-1}; cumulative dose 15 mg kg^{-1}) was compared with acute low dose of Doxo+Cipro (6+20 mg kg^{-1}) as shown in Fig. 5 (201±7.906 vs. 181.5±1.648 μmol L^{-1}). Similarly, significance was at par when both the low (6+20 mg kg^{-1}) and high doses (15+20 mg kg^{-1}) of Doxo+Cipro from acute group were compared (181.5±1.648 vs. 228.2±7.846 μmol L^{-1}) (Fig. 4).

DISCUSSION

Doxo a prototype drug from the active class of anticancer agents used to treat solid cancers and hematological malignancies (Gianni *et al*., 1997). While, Cipro belongs to wide spectrum antibiotic fluoroquinolones group and is successfully used in clinical practice to treat number of infections (Wolfson and Hooper, 1989) and as an antibacterial prophylactic as well as an anticancer agent in patients with superficial bladder cancer (Kamat and Lamm, 2004). Cipro acts by inhibiting the topoisomerase II. enzyme and same mechanism is followed by Doxo, combination of both these drug showed good correlation in inducing the cleavable complexes of topoisomerase II-DNA (Kamat and Lamm, 2004). Besides, both the drugs shares the same CYP450 enzymes for drug metabolism. So, this information leads us to hypothesis of drug-drug interaction, when combination of these drugs are prescribed in clinical practice, can result in unforeseen toxicity.

Several clinical studies have adopted the different dose schedules of Doxo alone or in combination with

other drugs to improve the anticancer activity. Similarly, dose dependent cardio-toxicity of Doxo led to the development of several animal models of chronic and acute cardio-toxicity (Bertazzoli *et al*., 2014; Herman *et al*., 2000). The present study was designed by keeping in view these information and divided into two major groups chronic and acute followed by the same doses of Doxo and Cipro but in different schedules as described above to study the Doxo concentration.

All the treated groups showed significant levels of Doxo in plasma of Sprague Dawley rats in comparison to control (Fig. 1). Minimum concentration was observed in low dose of Doxo alone from both chronic and acute groups (1 mg kg^{-1}; cumulative dose 6 mg kg^{-1} and 6 mg kg^{-1}, respectively) while, highest was observed in rats treated with high dose of Doxo+Cipro from both the chronic and acute groups (2.5+20 mg kg^{-1}; cumulative Doxo dose 15 and 15 mg kg^{-1}, respectively). As it is cleared from the results of our study the low or high dose of Doxo alone or in combination whether administered by following acute dose schedule or chronic, showed the same level of Doxo in plasma.

Whereas, the results of the present study revealed that dosing schedule did not cause significant effect on Doxo plasma levels. It can be concluded for sure that Doxo whether given as single i.p. injections or same dose divided into weeks showed the same plasma concentration. Literature showed that the chronic use of Doxo results into the accumulation of Doxo into cardiolipin that explains high concentration of Doxo in heart mitochondria (Lebrecht and Walker, 2007), uptake of drug plays an important role here. So, the present study indicated that the dose protocol does not cause effect on the plasma concentration but can affect the level of drug exposure to tissues or organs.

Since Doxo undergoes extensive hepatic metabolism (Sturgill *et al*., 2000) and Cipro may have a potential to interfere at Doxo disposition, significant interaction is possible. A strong interaction was observed at plasma levels when Doxo alone groups were compared with Doxo+Cipro groups. Rats treated with Doxo+Cipro showed significant increase in plasma concentration than that of Doxo alone. The increase in concentration can be subjected to the inhibition of Doxo metabolism. Usually the pharmacokinetic interactions are due to the inhibition or induction of enzymatic biotransformation of drugs (Ogu and Maxa, 2000).

As Doxo is metabolized by CYP3A4 isoenzyme (Baumhakel *et al*., 2001) and Cipro reversibly inhibits this isoenzyme (Badyal and Garg, 2000; Shahzadi *et al*., 2011). Cipro is also an inhibitor of CYP1A2 isoenzyme (Jerling *et al*., 1994). So, there is chance of drug interaction which confirmed by the findings of this study. The activity of these CYP450 enzymes is affected by different factors nutrition, genetics, environment (Bibi, 2008) and severe liver and celiac disease can decrease the activity of CYP3A4 isoenzyme (Pelkonen *et al*., 2008; Lang *et al*., 1996). All these factors are severally effected during the course of cancer chemotherapy and can lead to altered plasma concentration and ultimately drug effect. Besides the role of CYP450 enzymes, p-glycoproteins also plays a major role in drug-drug interaction (Greiner *et al*., 1999; Holtzman *et al*., 2006) and could be helpful in finding the pharmacokinetics, pharmacodynamics and toxicodynamics of the antibiotics in healthy and diseased individuals. Drug-transporting P-glycoproteins appears to have a greater impact on limiting cellular uptake of drugs from blood circulation into brain and from intestinal lumen into epithelial cells than on enhancing the excretion of drugs out of hepatocytes and renal tubules into the adjacent luminal space (Lin and Yamazaki, 2003). It has been found that absence of MDR1a P-glycoprotein affects the fate of Doxo chiefly by diminishing secretion of parent drug into the bile (Van Asperen *et al*., 2000) which can lead to increase in plasma concentration. Drug-drug interactions with antibacterial could be mediated by inhibition or induction of P-glycoprotein (Marchetti *et al*., 2007). There is no direct data available which could suggest the exact role of Cipro in inhibition or induction of P-glycoprotein but it has been found that Cipro did significantly inhibit the transport of rhodamine-123, a known P-glycoprotein substrate, in L-MDR1 cells (Park *et al*., 2011). Studies also revealed that Doxo is also a p-glycoprotein substrate (Shen *et al*., 2008). So further investigations are required to evaluate the drug interaction of Doxo and Cipro at p-glycoprotein levels.

Cipro increased the plasma concentration of Doxo at low doses in acute (6 mg kg^{-1}) and chronic (1 mg kg^{-1}; twice a week for 3 weeks; cumulative dose 6 mg kg^{-1}) group by 26 and 23%, respectively. While, the plasma concentration of Doxo at high doses in acute (15 mg kg^{-1}) and chronic (2.5 mg kg^{-1}; twice a week for 3 weeks; cumulative dose 15 mg kg^{-1}) group was increased by 16 and 14.3 % respectively. Interestingly, there is an increase in acute and chronic low of Doxo as compared to high chronic and acute doses but this change was statistically non-significant. It can be speculated that at high dose of Doxo, may involve certain other mechanism that interferes with Cipro pharmacokinetic behavior (ADME), so further research is required in this aspect.

Another striking outcome of our results was low acute dose of Doxo in combination with Cipro (6+20 mg kg^{-1}) showed same concentration as that of

15 and 2.5 mg kg^{-1} (cumulative dose 15 mg kg^{-1}) alone. However, the same dose of chronic group did not show similar behavior. The exact cause in not identified. but it can be speculated that 6+20 mg kg^{-1} Doxo+Cipro combination proved to be highly toxic high doses of Doxo alone in chronic and acute dose protocol.

The increase in plasma concentration after the combination therapy can results in unforeseen toxicities. Pharmacokinetic data showed good correlation between the electrocardiographic changes and the tissue distribution of the drug. Repeated acute myocardial damage by Doxo infusions is considered to be the cause of chronic cardiomyopathy with long-term administration (Lenzhofer *et al*., 1983). In another study paclitaxel infused over 24 h before Doxo given over 48 h of infusion was associated with higher plasmaconcentrations (Holmes *et al*., 1996). Another study confirms that when paclitaxel, cremophor and docetaxel when given together with Doxo alters the disposition of Doxo and increasing its levels in tissues including heart (Colombo *et al*., 1999). In another study the interaction of low-dose ranitidine with Doxo did not intensify Doxo-induced myelosuppression. Whereas, high-dose ranitidine enhanced doxorubicin-induced erythroid suppression. At cytochrome P-450-inhibitory doses, ranitidine's effects upon doxorubicin plasma pharmacokinetics are similar to those previously seen with cimetidine (Harris *et al*., 1988).

While, Cipro also confirmed that the change in pharmacokinetic behavior of other drugs when combination is given. Cipro significantly increased the plasma concentration of carbamazepine in healthy adult male volunteers (Shahzadi *et al*., 2011). In another study Cipro decreases the metabolism of itraconazole, most likely through inhibition of CYP3A4 (Sriwiriyajan *et al*., 2011). Clinical studies also showed that Cipro increased the response to bleeding in patients treated with anticoagulants (Ellis *et al*., 2000).

It can be concluded from the results of our present study that, there is a pharmacokinetic interaction, between Doxo and Cipro, which resulted into slow elimination of Doxo when given in combination to male Sprague Dawley rats. This may be due to the inhibition of CYP3A4 and CYP1A2 isoenzyme by Cipro or may be due to P-glycoproteins which also affect the drug-drug interaction when given in combination. It may be speculated that the striking anticancer activity seen with the combination of Doxo and Cipro but the increase in plasma concentration of Doxo may lead to certain unforeseen toxicities like increased in internal bleeding effect on kidneys and heart such interactions could have considerable consequences. Therapeutic outcome should be monitored closely when these two agents are concomitantly administered.

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