Journal of Clinical Toxicology
ISSN: 2161-0495

Alimoradi et al. J Clinic Toxicol 2011, S:6
DOI: 10.4172/2161-0495.S6-001

Research Article Open Access

Pretreatment of CAV Combination Chemotherapy with Tropisetron Shows Less Cardio and Neurotoxicity Side Effects in Rats

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Abstract

Tropisetron, a 5-HT3 antagonist receptor, is commonly used for the prevention of emesis following chemotherapy. Lines of evidence point to the anti-inflammatory and immune modulatory properties of tropisetron.

The current study aims to investigate whether tropisetron is able to prevent the cardiotoxicity and neurotoxicity induced by doxorubicin (DOX) and vincristine besides its anti emetic effect in a co-administration protocol, since this combination therapy is widely used in various combination chemotherapy regimens.

To investigate these effects, intraperitoneal co-administration of doxorubicin and vincristine in CAV combination therapy (Cyclophosphamide, Adriamycin and Vincristine) was used to induce neuro and cardiotoxicity and in treated group tropisetron was injected 1 h prior to combination therapy.

General conditions, mortality rate and body weight were measured during the experiment. Moreover, assessment of biomarkers of cardiac injury, ECG (Electrocardiogram) parameters and papillary muscle contractility force were done for evaluating of cardio protective effects of tropisetron. Similarly, hot plate, open field and nerve conduction velocity tests were used for investigation of neuroprotective effects of tropisetron against the side effects of this combination.

The findings in the present study indicated that tropisetron pretreatment led to significant decrease in levels of serum cardiac damage biomarkers, electrocardiographic changes and toxicities associated with this combination chemotherapy. Also, it improved behavioral and electrophysiological scores, papillary muscle contractility force and rats' general conditions.

Consequently, it is suggested that tropisetron is beneficial for the prevention of cardiotoxicity and neurotoxicity and could be considered as a new indication for alleviation of side effects of these drugs in combination therapies.

Keywords: Tropisetron; Doxorubicin; Vincristine; Cardio protective; Neuroprotective; Rat

Introduction

The co-administration of vincristine and doxorubicin is commonly prescribed in wide variety of combination chemotherapy regimens such as CAV (Cyclophosphamide, Doxorubicin and Vincristine), CHOP (Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone) and VAD (Vincristine, Adriamycin and Dexamethasone) as an effective treatment in a wide spectrum of human malignancies [1-3].

Although survival rate in patients received this combination therapy increases, most of patients experience some adverse effects including nausea, vomiting, alopecia, hematologic effects, peripheral neuropathy and cardiotoxicity [4-6]. Doxorubicin-induced cardiotoxicity and vincristine-induced neurotoxicity are two severe side effects which usually limit their indications in clinic [7,8].

Previous studies have manifested that doxorubicin-associated cardiotoxicity causes changes in electrocardiogram, heart weight loss and reduction in papillary muscle contractility force [8-10]. Some mechanisms proposed for this side effect are increase of oxidative stress, induction of systemic release of pro-inflammatory cytokines and calcium/calcineurin-dependent activation of the transcription factor NFAT (Nuclear Factor of Activated T-lymphocytes) in cardiac cells [11,12].

Besides, mixed sensory-motor neuropathy of vincristine is induced by infiltration of immune cells such as macrophages and lymphocytes into the injured region and up-regulation of pro-inflammatory cytokines [13,14]. These events result in increase of hot plate latency, decrease of total distance moved and nerve conduction velocity (NCV).

Tropisetron, a highly selective 5-HT3 receptor antagonist, is used as an effective and well tolerated antiemetic treatment for chemotherapy-induced emesis. It is commonly administered without special precautions to all patients received chemotherapy regimens and also it remains effective during multiple chemotherapy courses [15,16].

There is ample evidence that tropisetron exerts immune modulatory and anti-inflammatory properties [17]. Moreover, a new investigation has shown that tropisetron blocks NFAT-dependent signaling pathway

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Received February 03, 2012; **Accepted** March 15, 2012; **Published** March 18, 2012

Citation: Alimoradi H, Barzegar-Fallah A, Mohammadi-Rick S, Asadi F, Delfan B, et al. (2012) Pretreatment of CAV Combination Chemotherapy with Tropisetron Shows Less Cardio and Neurotoxicity Side Effects in Rats. J Clinic Toxicol S6:001. doi:10.4172/2161-0495.S6-001

and also it was suggested that calcineurin can be one of the main targets for the inhibitory effect of tropisetron in this pathway [18].

Fiebich et al. [17] have shown that in monocytes, lipopolysaccharide-stimulated secretion of both TNF-α (Tumor Necrosis Factor-alpha) and IL-1β (Interleukin-1 beta) was dose-dependently inhibited by tropisetron. Moreover, we have recently reported notable anti-inflammatory properties for tropisetron in an embolic model of stroke in rat. It significantly improved neurological deficits, diminished leukocyte transmigration into the brain, suppressed the inflammatory cytokine TNF-α, and dampened brain infarction and edema [19].

In the light of all previous evidence, this study was conducted to determine whether pretreatment of tropisetron can ameliorate mortality rate, general toxicity, cardiotoxicity and peripheral neuropathy related to combination of vincristine and doxorubicin. For evaluation of cardio protective effects of tropisetron, measurement of creatine kinase isoenzyme-MB (CK-MB), lactic dehydrogenase (LDH), creatine phosphokinase (CPK), and cardiac troponin T (cTNT) levels in serum were performed. Further, assessment of ECG parameters and papillary muscle contractility force were carried out. Similarly, hot plate, open field and nerve conduction velocity tests were used for investigation of neuroprotective effects of tropisetron against the side effects of this combination.

Materials and Methods

Ethics

These studies were conducted in accordance with protocols approved by the Ethics Committee of Tehran University of Medical Sciences and also adhered to guidelines of the US national institute of health (NIH publication no.85.23, revised 1985) guides for the care of lab animals.

Animals

Seventy two male Sprague Dawley rats (300_350g) were maintained in air filtered metabolic cages with temperature and humidity controlled environment with 12 hr light/dark cycle. Food consists of normal rat chow and water ad libitum. Animals were randomly divided into 3 study groups: (1) 30 rats received combination therapy of cyclophosphamide, doxorubicin and vincristine (CAV group); (2) 30 rats received cyclophosphamide+ doxorubicin+ vincristine+ tropisetron 5 mg/kg (CAV+ Tropi group); (3) 12 rats received saline as saline group.

Drug administration

Here drug administration was adjusted according to the CAV chemotherapy which contains three cycles and each cycle includes 3 weeks (one week for drug administration and two weeks for rest recovery). The doses of the drugs administered to rats were analogous to human doses after adjustment for the differences in surface area to weight ratio. Cyclophosphamide at the dose of 80 mg/kg, doxorubicin at the dose of 5.8 mg/kg and vincristine at the dose of 0.3 mg/kg were injected intraperitoneally (i.p.) at the first day of first week of each cycle (Figure 1). Tropisetron was dissolved in saline and injected at the dose of 5 mg/kg (i.p.) one hour prior to vincristine and doxorubicin administration. Through a preliminary study (not published), several doses of tropisetron from 1 mg/kg to 5mg/kg were evaluated for finding a dose that shows cardio- and neuroprotective effects and we found that the best dose here could be 5 mg/kg (i.p.).

Survival study and general condition

All rats were examined two times per week through the whole experiment to detect rate of mortality and clinical signs of general toxicity such as edema, cachexia, alopecia, gastro-intestinal disorders, hind limb weakness and weight loss.

Behavioral assessment

Rats were habituated to the testing procedures during the week prior to the experiment. At the last week of study (ninth week of study; (Figure 1), hot plate test for assessing sensory nerve function and open field test for detecting motor impairment were done.

In hot plate test, rats were placed on a 52± 0.2^{oc} heated plate (socrel hot-plate model DS37, Ugo Basile, Italy) and time spent until the first episode of heat sensitivity includes jumping, forepaw or hind paw licking. Similarly, in open field test animals were placed into an area (diameter 1.4 m) and their locomotion within the area were tracked over a 10 minuets period. Its data was recorded using a high resolution monochrome camera and analyzed with Ethovision software (v.8) and total distance moved was calculated.

Electrocardiographic studies (ECG)

To evaluate the track changes in heart rate and QT interval, ECG was monitored at the end of the study (ninth week of study; (Figure 1). Animals were anesthetized by sodium pentobarbital at the dose of 50mg/kg (i.p). Then, needle electrodes were inserted under the skin for the limb lead at position II and ECG was recorded by using a Power Lab data acquisition system (Chart .7. pro, AD Instruments, Power Lab). In this study Chart 7.pro (AD Instruments, Power Lab) software was used to analyze and quantify ECG segment durations.

Electrophysiological examination

After ECG recording, body temperature was monitored and maintained within normal limits. NCV was recorded in the left sciatic nerve (6 rats in each group) using power lab (MLT 1030/D, AD Instruments, Power Lab chart 7.pro) and the same stimulating and recording pin electrodes (AD Instrument, pin) as previously described [20]. In order to measure sciatic NCV, sciatic nerve was stimulated proximally and distally. Proximally, sciatic was stimulated by an active electrode located at the sciatic notch and the passive stimulating electrode was inserted into the dorsal aspect of the animal paravertebrally between the spinous processes of the lower lumbar vertebrae and the palpable posterior surface of the femoral head on the same side and situated at about 20 mm from the active electrode. After NCV recording, blood was collected from left ventricle and hearts were carefully dissected, kept in a modified today's tyrode solution and squeezed their blood out and then carefully weighed by a digital scale.

Left ventricular papillary muscle contractile study

At the last week of study 6 rats from each group were anesthetized by pentobarbital sodium (65 mg/kg) and their blood was collected through ventricular vein and hearts were excised and then left ventricular papillary muscles were isolated in a Modified today's tyrode solution including NaCl: 136.9 mM, $MgCl_2$: 2.5mM, KCl: 2.7mM, NaH_2PO_4: 0.4mM, $NaHCO_3$: 11.9mM, Glucose: 11.1 mM, $CaCl_2$: 2.5mM, buffered at pH: 7.4 and aerated with 95% O_2 and 5% CO_2. Left ventricular papillary muscle was held in an organ bath (AD Instrument, Power Lab, Spain) at 33°C and its contraction following a continuous electrical field stimulation was measured by an isometric force transducer (MLT 1030/D, AD Instruments, Power Lab, Spain) under a tension of 5 Newton, according to the method of Balaei et al. [21].

Biochemical study

To evaluate the effects of combination therapy of doxorubicin and vincristine on cardiotoxicity, the activity of serum LDH, CPK, CK-MB and cTNT were assessed. Activities of serum LDH, CPK, CK-MB using diagnostic kits from BioSystems S.A. (Barcelona, Spain) and cTNT by immunoassay kits (Elecsys 2010 Swiss/ Germany) were measured.

Statistical analysis

All values are expressed as mean ± SEM. For all tests, data were analyzed using one way analysis of variance (ANOVA) followed by the Tukey test (SPSS v.18). A P-value <0.05 was regarded as significant.

Results

The effects of tropisetron on mortality and general conditions

Sixteen rats in combination group (53.3%) and five rats in combination+ Tropi group (16.6%) died before termination of ninth week of study. All animals treated with CAV looked weaker and lethargic compared to other study groups. Also characteristic symptoms of general toxicity including yellow scruffy fur, red exudates around the eyes, enlarged abdomen, some gastro-intestinal disorders such as looseness and decrease in amount of stool, alopecia and hind limb weakness were observed. However, animals treated with CAV+ Tropi showed better general condition and fewer signs of toxicity. One week after the first drug administration (second week of study; Figure1) a significant decrease in body weight in CAV and CAV+ Tropi was determined compared with saline and this downward trend of body weight change continued until third cycle ($p< 0.001$). A significant difference in body weight was detected between CAV group and CAV+ Tropi group ($p=0.002$). Heart weights in only CAV treated animals were significantly lesser than saline group ($p= 0.007$). However, pretreatment of CAV with tropisetron prevented the heart weight loss as there was no significant change in heart weight of CAV+ Tropi group versus saline ($p= 0.281$).

Effects of tropisetron on behavioral studies

Hot plate: At the end of ninth week of study a marked hypoalgesia was observed in CAV group because hot plate latencies in this group significantly increased versus saline group ($p= 0.009$). Latencies in animals treated with CAV+ Tropi significantly changed compared with saline ($p= 0.043$) and also latencies in CAV+ Tropi group were significantly lesser than CAV group ($p= 0.022$; Figure 2a).

Open field: In animals received CAV chemotherapy regimen, gait disturbance, the ability of changing their path during movement and their spontaneous exploratory activities as indicators of motor impairment were reduced. Total distance moved significantly decreased in CAV receiving rats compared with saline (CAV group $p< 0.001$; CAV+ Tropi $p= 0.03$). Pretreatment of CAV with tropisetron significantly repaired gait disturbance (CAV+ Tropi group vs. CAV group $p< 0.001$; Figure 2b).

Effects of tropisetron on nerve conduction velocity

There was a significant reduction in sciatic nerve conduction velocity in both CAV and CAV+ Tropi groups in comparison with saline (CAV group $p< 0.001$, CAV+ Tropi $p= 0.036$). Figure 3 shows improvement in nerve conduction velocity in CAV+ Tropi group compared with CAV group ($p= 0.009$).

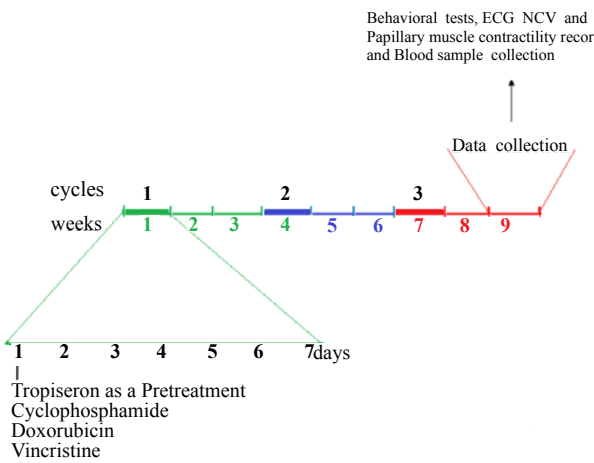

Figure 1: Cyclophosphamide, doxorubicin, vincristine and tropisetron treatment regimen. Drug administration contains three cycles and each cycle includes 3 weeks (one week for drug administration and two weeks for rest recovery). Cyclophosphamide at the dose of 80 mg/kg, doxorubicin at the dose of 5.8 mg/kg and vincristine at the dose of 0.3 mg/kg were injected intraperitoneally (i.p.) on day 1 of the first week of each cycle, while tropisetron at the dose of 5 mg/kg was injected 1 hour prior to administration of these drugs.

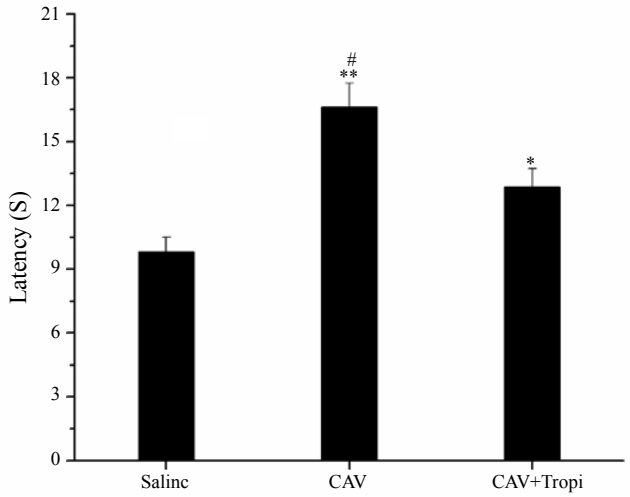

Figure 2a: Hot plate response of rats treated with CAV combination chemotherapy with or without Tropisetron. A significant increase in latencies was observed in CAV group and CAV+ Tropi group vs. saline ($p= 0.009$; $p= 0.043$ respectively) and also latencies between CAV+ Tropi and CAV group were significantly different ($p= 0.022$).

The effects of tropisetron on ECG changes related to combination therapy

In CAV group, some marked changes in ECG were detected such as bradycardia, Q-T, S-T and QRS prolongation and decrease in R and S amplitudes. Such abnormalities were ameliorated with tropisetron pretreatment. As table 1 shows, QT interval in rats received CAV significantly increased compared with saline (CAV group $p< 0.001$; CAV+ Tropi $p= 0.031$). Results show tropisetron could prevent ECG changes in CAV group and there was a significant difference between CAV group and CAV+ Tropi ($p= 0.022$). Moreover, the same results were detected about rat's heart rate as a significant decrease in heart rate was observed in CAV receiving groups versus saline group (CAV

p< 0.01 and CAV+ Tropi p= 0.045 vs. saline) and also tropisetron could repair the heart rate changes induced by CAV therapy.

The effects of tropisetron on serum markers of cardiac injury

Combination therapy caused a prominent cardiotoxicity, because serum levels of LDH, CPK, CK-MB and cTNT were significantly increased in CAV receiving group compared with saline (p<0.001) tropisetron obviously reduced concentration of these biochemical markers in CAV+ Tropi compare with CAV group (P<0.001; table 2).

The effect of tropisetron on left ventricular papillary muscle contraction

Figure 4 shows that papillary muscle contractility force in CAV receiving groups significantly decreased compared to saline (CAV group P< 0.001; CAV+ Tropi group p=0.01). A significant increase in papillary muscle contractility in CAV+ Tropi group versus CAV group shows that tropisetron can ameliorate this adverse effect (P= 0.038).

Discussion

In this study, we examined the protective effects of tropisetron pretreatment, which is used as an anti emetic agent in chemotherapy, against cardiotoxicity and neurotoxicity side effects of combination therapy with vincristine and doxorubicin (Adriamycin) in a rat model. Co-administration of these two drugs is commonly prescribed in different combination chemotherapy regimens such as VAD [1], CHOP [2], CAV [3], VAMP (vincristine, Adriamycin and Methylprednisolone) and C-VAMP (VAMP and cyclophosphamide) [22].

The findings in the present study showed for the first time that pretreatment of experimental animals with tropisetron 5mg/kg 1 hour prior to drugs administration robustly decreased toxicities associated with this combination chemotherapy. Also, this intervention with tropisetron completely diminished mortality rate, body weight loss, and improved rats' general conditions.

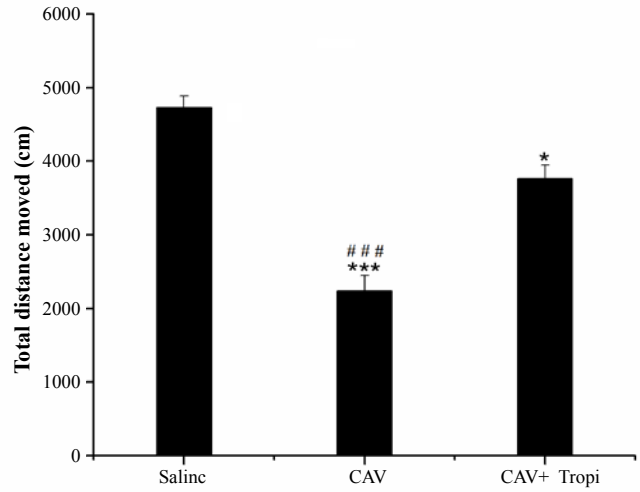

Figure 2b: Total distance moved within the open field area (diameter 1.4 meter) was assessed over 10 min. It significantly decreased in CAV and CAV+ Tropi groups compared to saline (p<0.001; p= 0.03 respectively). Moreover a significant difference between CAV and CAV+ Tropi groups was detected (p<0.001). Data are presented as mean± S.E.M of 6 rats.
*p< 0.05; **p<0.01; ***p<0.001 compared to saline group.
#p<0.05; ###p<0.001 compared to CAV group.

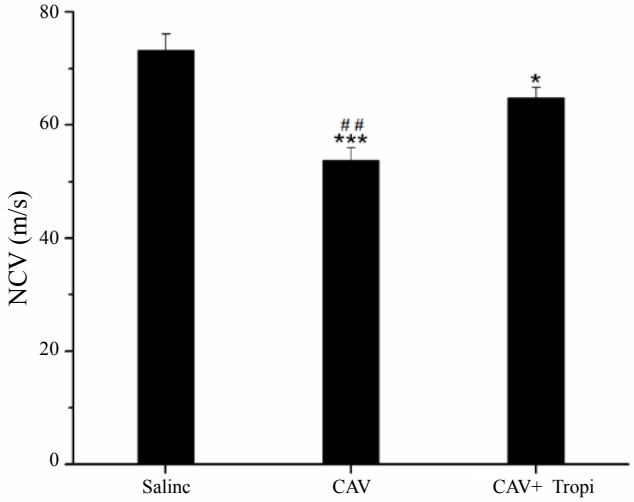

Figure 3: Sciatic nerve conduction velocity values recorded from rats treated with CAV with or without Tropisetron. A significant reduction between CAV or CAV+ Tropi group and saline was detected (CAV group p< 0.001, CAV+ Tropi p= 0.036). Furthermore the difference between CAV+ Tropi and CAV group was significant (p= 0.009). Data are presented as mean± S.E.M of 6 rats.
*p< 0.05; ***p<0.001 compared to saline group.
##p<0.05 compared to CAV group.

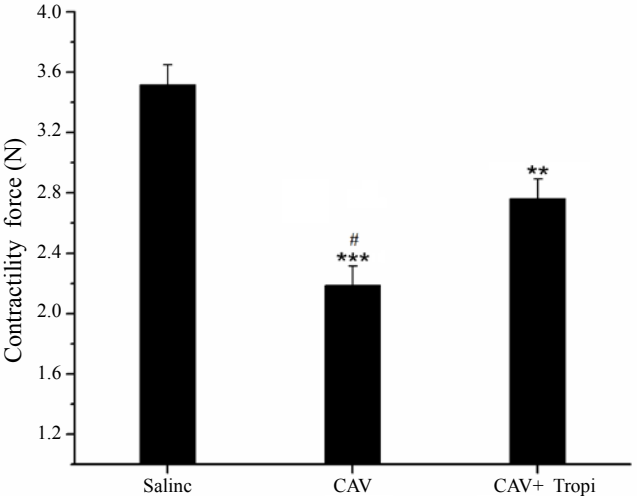

Figure 4: Comparison of papillary muscle contractile force (N) in saline, CAV and Tropi+ CAV groups. Contractility force in CAV and Tropi+ CAV groups decreased vs. saline group (CAV group P< 0.001; CAV+ Tropi group p=0.01). Further tropisetron was able to repair the cardiotoxicity- induced by CAV as contractility force in group receiving tropisetron increased in comparison with CAV group (p= 0.038). Data are presented as mean± S.E.M of 6 rats.

Study groups	Heart rate	Q-T interval
Saline	322.0± 5.9	61.2± 3.6
CAV	267.1± 6.4 **	93.8± 5.2***
CAV+ Tropi	290.2± 5.7 *#	77.2± 2.5 *#

CAV chemotherapy led to bradycardia and Q-T interval prolongation while tropisetron pretreatment could prevent heart rate and ECG changes in CAV+ Tropi group. Values are the mean ± S.E.M of 6 rats.
*p< 0.05; **p<0.01; ***p<0.001 compared to saline group.
#p< 0.05 compared to CAV group.

Table 1: Effects of tropisetron pretreatment on CAV combination chemotherapy-induced alterations in (A) heart rate and (B) QT interval.

Study groups	LDH	CPK	CK-MB	cTNT
Saline	129.6 ± 8.1	211± 16.2	103.8±8.6	0.085± 0.04
CAV	363.7± 8.7	740.8± 19.1	282.7±9.6	0.82± 0.05
CAV+ Tropi	192.8± 12.2###	309.4± 18.4###	180.0±10.0###	0.45± 0.07###

Tropisetron obviously reduced serum concentration of LDH, CPK, CK-MB and cTNT increased following CAV- induced cardiotoxicity. Data are presented as mean ± S.E.M of 6 rats.
###p<0.001 CAV+ Tropi group compared to CAV group.

Table 2: The effect of pre-treatment with tropisetron (Tropi) on CAV combination chemotherapy- induced alterations in serum biomarkers of cardiac injury; (A) lactate dehydrogenase (LDH), (B) creatine phosphokinase (CPK), (C) creatine phosphokinase isoenzyme-MB (CK-MB) and (D) cardiac Troponin T (cTNT).

According to our data, a significant increase in hot plate latency as an indicator of sensory neuropathy and a decrease in total distance moved as an indicator of abnormal locomotion activity showed neuropathy potentially induced by vincristine. The detected decrease in NCV in sciatic nerve confirmed this nerve injury. Moreover, our results indicated a severe cardiotoxicity after this co-administration in rats, since ECG was prominently changed (ECG changes included bradycardia, Q-T, S-T and QRS prolongation and decrease in R and S amplitudes), biomarkers levels of cardiac injury in serum were significantly increased and heart weight and papillary muscle contractility were significantly reduced in comparison with saline group.

A single injection of tropisetron before combination chemotherapy counteracted the increase in serum level of biomarkers released from damaged myocytes and they are used as sensitive indicators for doxorubicin-induced cardiac dysfunction [23,24]. These biomarkers include CK-MB, LDH, CPK, and cTNT. Also, tropisetron protected heart against negative effects of doxorubicin on papillary muscle contractility and loss of heart weight, since doxorubicin causes cardiac fiber loss and myocardial necrosis which follows by reduction of heart weight and impairment of contractility [25-28]. Further, ECG abnormalities, behavioral and electrophysiological tests were improved with tropisetron.

One of the proposed mechanisms for doxorubicin cardiotoxicity is induction of intracellular calcium overload that induces cardiac cells apoptosis via activation of calcineurin/NFAT signaling pathway in cardiomyocytes [12,29]. Elevation of intracellular calcium activates calcineurin that leads to dephosphorylation of NFAT which plays an important role as a transducer of the cardiac hypertrophic response [12,30-32]. Also a recent report has indicated that NFAT can be a crucial transcription factor in promoting doxorubicin-induced cardiomyocytes apoptosis [12].

In addition to cardiomyocytes, the raising of intracellular calcium level in injured nerve can lead to calcineurin activation and finally end in neuronal cell apoptosis [33].

Besides, *in vitro* and *in vivo* studies have indicated that repeated systemic injection of vincristine damages Schwann cells and dorsal root ganglion (DRG) neurons [34,35]. Release of inflammatory cytokines IL-1β, IL-6 (Interleukin-6), and TNF-α from damaged Schwann cells, macrophage invasion into the injured nerve and IL-2 (Interleukin-2) secretion from T-cells cause neuro inflammation, leading to neuropathic pain [36]. These events culminate in sensory-motor neuropathy that is the limiting factor of use in patients treated with vincristine [37].

The possible protective effects of tropisetron can be presented through inhibition of calcineurin/NFAT-dependent signaling pathway [18].

Calcineurin (CN) is a widely distributed Ca^{2+}-calmodulin-dependent protein phosphatase 38 that plays a key role in calcium-dependent death pathways in thymocytes [38] and neural tissues [39] and participates in an apoptotic death pathway activated by TNF [33].

Since, calcineurin plays an important role in neural damage and has been suggested to be a new molecular target for tropisetron; inhibition of its activation by tropisetron represents one possible mechanism for neuroprotective effects of this drug [18].

Moreover, tropisetron effectively inhibits AP-1 (the activator protein 1) and NF-κB (nuclear factor-kappa-B) transcriptional activities that the coordinated activation of them with NFAT is necessary for the transcriptional activity of the IL-2 gene 18. In cardiomyocytes, activation of the transcription factor NF-κB in response to DOX plays a pro-apoptotic role 29. In the other side, in tumour cells its activation exerts an anti-apoptotic effect [40]. It shows the dual role of NF-κB in regulating apoptosis [12].

Several studies have demonstrated that tropisetron has immune modulatory and anti-inflammatory properties. Also it has shown to be an effective inhibitor of lipopolysaccharide-stimulated secretion of TNF-α and IL-1β in monocytes and serotonin-induced prostaglandin E2 release from synovial cells and it modulates T-helper1 cytokines in patients with musculoskeletal diseases [17,41,42].

The above mentioned mechanisms could be responsible for neuro and cardio protective effects of tropisetron. Therefore, tropisetron pretreatment, a well tolerated and safe antiemetic drug for chemotherapy, can be considered as a new medication for prevention of cardiotoxicity and neurotoxicity side effects of doxorubicin and vincristine used in various combination chemotherapy regimens.

Acknowledgement

The collaboration of Dr. Mehrak Javadi-Paydar in expert technical assistance is gratefully acknowledged by the authors. This study was supported by a grant from Tehran University of Medical Sciences.

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This article was originally published in a special issue, **Neuropharmacology & Neurotoxicity** handled by Editor(s). Dr. Terreia S Jones, University of Tennessee Health Science Center, USA