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Does Dipyridamole Attenuate Whole Body γ-rays-Induced Oxidative Damage in Male Rats?

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DIPYRIDAMOLE (DP), a pyrimido-pyrimidinic derivative is a phosphodiesterase inhibitor, chemically related to adenosine and inhibits the cellular uptake of adenosine with antithrombotic and vasodilation actions. The aim of this study is to evaluate the effect of subcutaneous administration of DP (100 mg/ kg body wt, 5 times/ week for 3 weeks) on oxidative stress in 6 Gy γ-irradiated rats delivered at a single dose.

Irradiated group revealed significant increase of serum malondialdehyde (MDA), advanced protein oxidation products (AOPP), protein carbonyl (PCO), nitric oxide (NO), urea, triglycerides and cholesterol contents. While, there was a significant decrease of blood reduced glutathione (GSH), erythrocytes (RBCs) and platelets counts, haemoglobin content (Hb), haemotocrit value (Hct), count of total leukocytes, neutrophils and lymphocytes.

Irradiated DP treated rats showed significant improvement in the radiation-induced disorders in all tested parameters. The current study highlights DP as promising agent which could strengthen the defence mechanisms of the physiological systems against the oxidative stress induced by ionising irradiation.
Keywords: dipyridamole, γ-rays, oxidative damage, rats.

The absorption of ionising radiation by living cells can directly disrupt atomic structures, producing chemical and biological changes. It can also act indirectly through radiolysis of water, thereby generating reactive chemical species that may damage nucleic acids, proteins and lipids (Hall and Giaccia, 2006). Together, the direct and indirect effects of radiation initiate a series of biochemical and molecular signalling events that may repair the damage or culminate in permanent physiological changes or cell death. Oxidative changes, including protein carbonisation, lipid peroxidation, and enhanced rates of

spontaneous gene mutations and neoplastic transformation (Buonanno *et al.*, 2011) responsible for most of the effects of ionizing radiation in mammalian cells, occur during or shortly after the radiation exposure which continue to arise for days and months after the initial exposure (Petkau, 1987). Since the beginning of the nuclear era, despite extensive research on the development of radio protectors from natural and synthetic compounds, success has been limited. Therefore, attempts have been made to improve the therapeutic effect of radiotherapy by minimizing normal tissue damage to acceptable level by using synthetic compounds.

DP, a pyrimido-pyrimidinic derivative, chemically related to adenosine, inhibits the cellular uptake of adenosine with antithrombotic and vasodilation actions (Di Salvo *et al*., 1996) and is effective in the secondary prevention of cerebrovascular disease (Diener *et al*., 1996). It has been suggested to inhibit platelet phosphodiesterase and stimulate the release of prostacyclin (Constantini *et al.,* 1990). Pospisil *et al*. (1993) reported that the elevation of extracellular adenosine induced radio protective action in mouse caused by the effect of the treatment on the cardiovascular system and enhanced regeneration of haematopoietic stem cells. At clinically relevant concentrations, DP protects erythrocyte membranes from oxidation and spares the antioxidant power of erythrocytes (Kusmic *et al*., 2000). Furthermore, DP suppresses oxygen free radical formation in platelets and endothelial cells and improves cellular redox status (Chakrabarti *et al.,* 2005). This work establishes the ability of DP to attenuate the oxidative damage induced by a single dose of 6 Gy γ-rays.

Material and Methods

Animals

Forty eight mature male Swiss albino rats weighing from 130 to 150 g, were obtained from the Nuclear Research Centre, Inchas, Egypt. The animals were maintained on a commercial standard pellet diet and tap water *ad libitum*.

Irradiation and DP treatment

Whole body γ-irradiation was performed using a Canadian ^{137}Cs Gamma Cell-40 at NCRRT, Egypt; at a dose rate 0.43 Gy/ min. Rats were exposed to 6 Gy applied as a shot dose to induce drastic radiobiological changes.

DP (Sigma, St. Louis, MO, USA) was dissolved in 0.4% tartaric acid and injected subcutaneously (s.c.) at a dose of 100 mg /Kg 5 times/ week (Ueda *et al.*, 1996), as the mean peritoneal half-life for total extractable DP was 3.3± 1.9h (Chan *et al*., 1988).

Animals were divided into 1- Untreated control group. 2- Animals s.c. treated with 0.4% tartaric acid (5 times/ week for 3 weeks). 3- Animals were s.c. treated (5 times/ week for 3 weeks) with DP (100 mg/ kg). 4- Animals irradiated at a dose of 6 Gy γ-rays. 5- Animals irradiated at a dose of 6 Gy γ-rays and 2 h post irradiation, were s.c. treated (5 times/ week for 3 weeks) with that 0.4% tartaric acid. 6- Irradiated rats at a dose of 6 Gy, that were s.c. administered 5 times/ week for 3 weeks with DP (100 mg/ kg). Animals were scarified according to the ethical considerations of animal rights at the end of experiment (22 days).

Collection of blood and tissue samples

At the end of experiment, animals were anesthetized with ether. Two blood samples were immediately collected by heart puncture. The first sample was collected in heparinised tube for haematological assays. The second blood sample was centrifuged (1000 xg for 10 min), collected in test tubes with screw caps and serum was stored at -20°C until analyzed.

Haematological and biochemical assays

The first heparinised blood sample was used for RBCs and platelet counts, Hb, Hct, total leukocyte and absolute neutrophil and lymphocyte counts were analysed by automated blood counter (coulter model T 450 x, Contronics Co., USA). Blood GSH content was measured according to Beutler *et al.* (1963). Serum MDA was estimated according to Yoshioka *et al*. (1979). AOPP was measured according to Witko-Sarsat *et al.* (1998). Protein-carbonyl value was determined according to Reznick and Packer (1994), using Sigma-Alderch chemical Co. (St Louis, USA). NO level was measured using Griess reagent, Calbiochem kit, according to Green *et al.* (1982). Serum cholesterol and triglycerides were measured using kits of Spinreact Company, Spain, according to Richmound (1973) and Fossati and Prencipe (1982), respectively. Serum total proteins and urea were determined by kits according to the methods of Lowry *et al.* (1951) and Tobacco *et al.* (1979), respectively.

Statistical analysis

Data was expressed as means± S.E. Comparisons among groups (n= 8) were performed by one-way analysis of variance (ANOVA) followed by Duncans post-test. Differences were considered statistically significant at $P< 0.05$ (Zar, 1999).

Results

Duncans multiple range test revealed non significant differences between control groups as well as tartaric acid and DP treated groups for all estimated parameters except for triglycerides and cholesterol contents in DP group, which showed significant decrease as compared with control group.

TABLE 1. Serum NO, AOPP, PCO and urea in different animal groups.

Groups	NO µmol/ l	AOPP µmol/ l	PCO nmol/ mg protein	Urea mg/dl
Control	78.83± 3.0[b]	49.18± 3.35[b]	0.66± 0.07	54.02± 6.01[b]
Tartaric acid	77.6± 2.95[b]	47.28± 4.1[b]	0.67± 0.06	55.02± 7.0[b]
DP (100mg/kg)	81.17± 4.4[b]	38.75± 3.9[b]	0.61± 0.04	46.02± 5.01[b]
Irrad (6Gy)	97.5± 2.19[a]	63.84± 5.27[a]	1.42± 0.12[a]	67.02± 7.01[a]
Irrad+ Tartaric acid	96.33± 3.17[a]	62.52± 3.7[a]	1.44± 0.13[a]	66.02± 5.9[a]
Irrad+ DP	85.0± 1.97[b]	48.199± 3.6[b]	0.99± 0.05[b]	57.5± 6.3[b]

a:significant with control. b:significant with irradiated group. Mean± S.E. significantly at $P< 0.05$.

Serum AOPP, PCO, urea, NO values were increased significantly in animals exposed to 6 Gy γ-rays, compared to control group. While treatment with DP post irradiation has shown significant decreased in serum AOPP, PCO, NO and urea concentrations, compared to γ-irradiated group, Table 1.

TABLE 2. Blood GSH, serum lipid peroxidation, cholesterol and triglycerides in different animal groups.

Groups	GSH mg/dl	MDA nmol/ L	Cholesterol mg/dl	Triglycerides mg/dl
Control	32.28± 2.1[b]	27.9 ± 1.41[b]	62.44± 2.0[b]	96.4± 2.4[b]
Tartaric acid	33.26± 3.34b	27.35 ± 1.2[b]	62.15± 2.58[b]	94.5± 2.3[b]
DP (100mg/kg)	33.31± 3.7[b]	29.75± 2.5[b]	41.73± 3.0[ab]	88.41± 2.29[ab]
Irrad (6Gy)	21.98± 1.11[a]	46.62± 4.2[a]	95.16± 6.2[a]	137.4± 5.0[a]
Irrad+ Tartaric acid	23.83± 1.2a	40.34± 3.15[a]	94.57± 4.9[a]	134.0± 4.9[a]
Irrad+ DP	29.78± 2.1[b]	29.74± 2.34 [b]	82.16± 3.5[a,b]	108.8± 5.8[b]

Legends as in Table 1.

The blood GSH decreased significantly in irradiated group, Table 2, while MDA, cholesterol and triglycerides contents significantly increased in γ-irradiated group compared control and non-irradiated groups. DP (100 mg/ kg 5 times/ week for 3 weeks) treatment post irradiation has been significantly reduced the severity of changes in comparison to irradiated rats.

TABLE 3. RBCs and platelets counts, Hb content and Hct % in different animal groups.

Groups	RBCs $x10^6$ µL	Hb g/dl	Hct %	Platelets $x10^3$µL
Control	6.49± 0.0.17[b]	15.15± 0.33[b]	33.37± 0.41[b]	448± 18[b]
Tartaric acid	6.56± 0.20[b]	15.06± 0.45[b]	33.94± 1.1[b]	480± 38[b]
DP (100mg/kg)	5.79± 0.18[b]	14.06± 0.45[b]	31.32± 0.91[b]	504± 37[b]
Irrad (6Gy)	4.61± 0.33[a]	11.02± 0.49[a]	26.68± 0.82[a]	343± 19[a]
Irrad+ Tartaric acid	4.47± 0.34[a]	11.84± 0.41[a]	25.33± 0.92[a]	329± 17[a]
Irrad+ DP	5.33± 0.10[ab]	12.29± 0.34[ab]	29.61± 1.15[ab]	442± 46[b]

Legends as in Table 1.

A significant depression of RBCs and platelet counts, Hb, Hct was observed in irradiated groups. DP treatment before γ-irradiation at 6 Gy has significantly increased the blood parameters compared to the irradiated group, Table 3.

TABLE 4. Leukocytes, neutrophils and lymphocytes counts in different animal groups.

Groups	Leukocytes	Neutrophils	Lymphocytes
	$x10^3$ µ		
Control	11.62± 0.68[b]	4.63± 0.53[b]	5.93± 0.75[b]
Tartaric acid	11.53± 0.72[b]	4.05± 0.82[b]	5.70± 0.65[b]
DP (100mg/kg)	12.36± 0.62[b]	5.6± 0.79[b]	6.08± 0.17[b]
Irrad (6Gy)	5.46± 0.53[a]	2.75± 0.16[a]	2.7± 0.41[a]
Irrad+ Tartaric acid	6.22± 0.46[a]	2.78± 0.39[a]	3.28± 0.17[a]
Irrad+ DP	7.26± 0.66[ab]	3.72± 0.27[b]	4.32± 0.58[ab]

Legends as in Table 1.

Animals received γ-rays showed a significant decrease in blood leukocytes (total, neutrophil and lymphocyte) count, compared to control group. DP treatment to irradiated animals has significantly reduced changes in total and absolute leukocytes counts in comparison to γ- irradiated animals. Table 4.

Discussion

The balance between oxidation and reduction reactions determines cellular redox homeostasis and plays an essential role in numerous signalling cascades including those associated with proliferation, inflammatory responses, apoptosis, and senescence. Reactive oxygen and nitrogen species (ROS; RNS) are invariable components of aerobic metabolism and are key contributors to cellular redox (Tew *et al.,* 2011). DP lowers formation of ROS in platelets and endothelial cells, and improves cellular redox status (Chakrabarti *et al.,* 2005), prevents membrane and mitochondrial lipid peroxidation as well as oxidative modification of low-density lipoprotein (Iuliano *et al.,* 1996) and is an effective agent for protection of neurons from oxidative stress (Farinelli *et al.* 1998). DP serves as an effective scavenger in both the aqueous and lipid phases (Iuliano *et al.,* 1995).

In the present study, serum AOPP, NO, urea and protein carbonyl levels in irradiated group were significantly increased in comparison with control. Radiation induced ROS may result in oxidative damage. Oxidative damage to proteins renders them prone to segregation and degradation. Further, carbonisation damage is un-repairable, which may impair the activity of key proteins essential for healthy survival (Nystrom *et al.,* 2005). Radiation disrupt protein structures with consequent loss of functions, change the transport properties of lipid bilayers, the trans membrane potential of both plasma and nuclear membranes, and cause the accumulation of cytotoxic products (Ziegler and Wessels, 1998).

In treated irradiated group, DP has significantly improved the alterations that occurred in AOPP, NO, urea and protein carbonyl parameters as compared with irradiated group. DP modulation effects may be attribute to DP-antioxidant properties. The peroxyl radical scavenging activity of DP was confirmed in human erythrocytes by Kusmic *et al.* (2000). The antioxidant properties of DP suppress the endogenous release of vascular reactive oxygen and inflammatory species in vascular cells (Chakrabarti *et al.,* 2005). DP scavenges oxygen radicals and protects from free radical-induced peroxidative damage in different tissues in systems which peroxidise fatty acids (Iuliano *et al*., 1989) and in human liver membranes (De La Cruz *et al*., 1992). In the present work, it is

reasonable to speculate that all these explanations together are involved in the modulatory role of DP against irradiation induced-oxidative damage in rats.

In the current study, significant inhibition of blood GSH content and significant elevation MDA, triglycerides and cholesterol levels were observed in γ-irradiated groups compared with control groups**.** The depletion in blood GSH level might result from diffusion through impaired cellular membranes and/ or inhibition of GSH-synthetase and glutathione reductase enzymes (Zahran *et al.*, 2006). Lipid metabolites were elevated in serum of irradiated animals which could be attributed to acceleration of other pathways of cholesterol formation in the liver and other tissues (Pulikova and Sedlakova, 1988). Free radicals destroy the cell membranes, enhance cholesterol release and increase the lipid peroxidation (Karbowink and Reiter, 2000). The presence of polyunsaturated fatty acids in cellular membrane makes it highly susceptible for oxidative damage induced by ROS generated through radiation exposure, yielding cytotoxic break dawn lipid peroxides such as MDA (Gago-Dominguez *et al.*, 2005).

Gamma-irradiation-induced MDA elevated levels were prevented by DP and restored the GSH levels significantly, pointing to an antioxidant effect of DP, as a phosphodiesterase inhibitor. The molecular structure of DP allows it to accept electrons, thus functioning as a free radical scavenger and antioxidant (Kim and Liao, 2008).

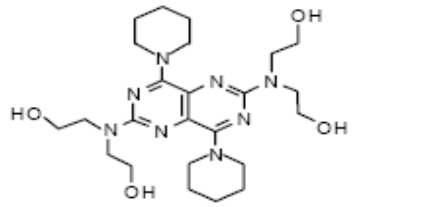

Fig. 1. Chemical structure of dipyridamole.

Serum cholesterol and triglycerides levels in γ-irradiated animals at 6Gy were increased as compared with control group, DP (100mg /kg) treatment, ameliorated the increase in cholesterol and triglycerides levels in γ-irradiated animals. DP prevents membrane and mitochondrial lipid peroxidation as well as oxidative modification of low-density lipoprotein (Iuliano *et al*., 1996) and

lower formation of ROS in platelets and endothelial cells, and improves cellular redox status. The antioxidant effect DP may be ascribed to its partition in the lipid phase of the mitochondrial membrane and not to a specific interaction with membrane proteins (Chakrabarti *et al*., 2005). Further, in the present study, this attenuation effect of DP may be due either to a direct inhibition of the propagation steps or a scavenger effect on the free radical species that would result from γ-irradiation.

The current results show that γ-irradiation at 6 Gy caused suppression in RBCs and platelets counts, Hct and Hb as well as total WBCs, lymphocyte and neutrophil counts compared to the control groups. These results are in accordance with those of Salama (2011) and Hanafi *et al*. (2009). Wang *et al.* (2006) reported that exposure of C57BL/6 mice to 6.5Gy induced a quantitative and qualitative reduction of haematopoietic stem cells (HSC), resulting from induction of senescence and impairment of HSC self-renewal via activation of the specific cellular pathways. This is complicated by thrombocytopenia and concomitant haemorrhages, besides effects in adaptive immune system resulting from apoptosis of lymphocytes and deficient lymphopoiesis (Wilkins *et al.*, 2002). Ionizing radiation is known to induce oxidative stress through generation of ROS and RNS and resulting in imbalance of the pro-oxidant and antioxidant activities (Srinivasan *et al.*, 2007).

DP treatment ameliorated significantly the decrease in all blood parameters in γ-irradiated animals. Hofer *et al*. (2002) suggested a positive role of DP and adenosine monphosphate, in supporting regeneration from severe γ-rays myelo suppression in mice. These positive effects of the tested treatment are due to increased restoration of the pools of haematopoietic progenitor cells in the bone marrow and spleen in early time intervals following termination of the treatment.

DP binds non-covalently to the most abundant protein on the RBC membrane with about a million copies per cell (van Steveninck *et al*., 2000). In agreement with our results, it has been reported that DP exerts an inhibitory effect on lipid peroxidation and acts as a scavenger of superoxide anion, hydroxyl radical and peroxyl radical (Iuliano *et al*., 1995). The radiation-induced lipid peroxidation in mouse liver and spleen was inhibited by DP pre-

treatment 1 hour before irradiation (Udea *et al*., 1996). Thus DP has selective protection to RBCs against oxidative damage. DP inhibits adenosine uptake and adenosine deaminase, thus increasing its extra cellular adenosine and cyclic adenosine mono-phosphate formation.The latter modulates intracellular levels by activating adenylate cyclase activity and inhibiting phosphodiesterase activity that trigger haematopoietic stem cells to enter the cell cycle and vascular growth (Adair, 2005). DP improves micro-vascular function by increasing RBC deformability and reducing blood viscosity. In addition, it has anti-oxidant and anti-inflammatory properties that provide protection to the microvasculature (Bhavsar and Rosenson, 2010). The study could be concluded that DP may be applied to minimize radiation damage and attenuate the side effects of radiotherapy. These results observed in rats need to be confirmed in other experimental models, but could become a part of the rationale of further randomised clinical trails in patients treated by radiotherapy.

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هل يحسن الداى بيريدامول التلف ألتأكسدي الذي تحدثه أشعة جاما في ذكور الجرذان؟

صفوت فريد سلامه و نعمة محمد الفاتح

قسم بيولوجيا الإشعاع ، المركز القومي لبحوث وتكنولوجيا الإشعاع ، ص. ب.بريدك ٢٩ مدينة نصر ، مصر.

يعرف الداى بيريدامول المثبط لإنزيم الفوسفوداي استيراز بالانابليت-٧٥ كماانه يثبط الامتصاص الخلوى للادنوسين وله تأثير مانع لتكوين الجلطة وموسع للأوعية . ولقد هدفت هذه الدراسة إلى تقييم كفاءة الداى بيريدامول عند إعطاءه للجرذان بالحقن تحت الجلد للحد من أضرار الإجهاد التاكسدى للتعرض لجرعة واحدة مقدرها ٦ جراى من أشعة جاما .

قسمت الفئران إلى ستة مجموعات : ١-مجموعة ضابطة ، و٢- مجموعة تم حقنها تحت الجلد بحمض الطرطريك بتركيز ٠.٤% و٣- مجموعة عولجت بالعقارمذاب في محلول ٠.٤% حمض طرطريك بجرعة (١٠٠ ملليجرام/ كيلوجرام من وزن الجسم ٥ مرات أسبوعيا لمدة ٣ أسابيع)٤- مجموعة عولجت بحمض الطرطريك بتركيز ٠.٤% وعرضت لجرعة واحدة مقدارها ٦ جراي من أشعة جاما ،٥- مجموعة عرضت لجرعة واحدة مقدارها ٦ جراي من أشعة جاما و مجموعة عرضت لأشعة جاما بنفس الطريقة السابقة و حقنت تحت الجلد بالعلاج بعد التشعيع بساعتين (١٠٠ ملليجرام/ كيلوجرام من وزن الجسم ٥ مرات أسبوعيا لمدة ٣ أسابيع).

تم اختيار بعض المعايير كدلائل للإجهاد التاكسدى الناتج عن الإشعاع و هي مالون ثنائي الالدهيد وناتج أكسدة البروتين المتقدم و الكاربونيل بروتين و اكسيد النيتريك و الجلوتاثيون المختزل و اليوريا والجليسريات الثلاثية والكولسترول و العد الكلى و المطلق للخلايا الدم البيضاء و العد الكلى لخلايا الدم الحمراء والصفائح الدموية والهيموجلوبين والهيماتوكريت .

أظهرت نتائج القياسات في مجموعة الفئران التي عرضت للإشعاع وجود زيادة معنوية في مستوي كل من مالون ثنائي الالدهيد وناتج أكسدة البروتين المتقدم و الكاربونيل بروتين واكسيد النيتريك و اليوريا والجليسريات الثلاثية والكولسترول . كما أوضحت النتائج وجود نقص معنوي بمستوي كلا من الجلوتاثيون المختزل و في كل مؤشرات الدم في نفس المجموعة.أما نتائج القياسات بالمجموعة التي عرضت للإشعاع بالتزامن مع الحقن بالداى بيريدامول حدث تحسن وتعديل ملحوظ في كل القياسات في اتجاه استعادة تلك المعايير لمستوياتها الطبيعية. يوصي الدارسون بأن المادة التي تمنع أو تقلل الإجهاد التأكسدي الناتج عن الإشعاع الجامى قد تكون من الوسائل المناسبة للحد من تدمير الخلايا الحية المعرضة للإشعاع.