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Treatment of Cisplatin Haematotoxicity with Lasix or Selenium or Both in Adult Male Rabbits

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Abstract: The effect of cisplatin (8 mg/kg b.wt. i.p) on the haemopoietic system alone or in combination with lasix (0.25 mg/kg b. wt, i.m) or sodium selenite (20 μmol/kg b. wt. i.m) or both were discussed in the male albino rabbits for 6 weeks. The IP injection of cisplatin induced a marked decreases in body weight, in the number of red blood cells; haemoglobin contents; haematocrit values and iron levels in the plasma, accompained by an elevations in total bilirubin. Co-administration of lasix with cisplatin partially improved the loss of body weight and the treatment of haematological parameters. Co-administration of selenium with cisplatin partially improved the loss of body weight and completely improved the haematological parameters. Treatment of cisplatin with lasix or sodium selenite or both completely prevented haematological toxicity of cisplatin and the animals restored their normal weight.

Key words: cisplatin, lasix, selenium, rabbits.

Introduction

Adverse effect on cells of the haemopoietic system represent some of the most serious and common side effects of drugs (Firkin, 1995).

Cis-diamminedichloro platinum (II) (cisplatin) was introduced as a tumor chemotherapy in 1970. It has been found to be very effective in the treatment of wide range of tumor diseases (Rosenberg, 1975; Corder *et al.*, 1977; Prestayko *et al.*, 1980; Zamble *et al.*, 1998). Rosenberg *et al.* (1969) first reported the activity of cisplatin against sarcoma 180 and L-1210 mouse leukemia. Kociba *et al.* (1970) have shown a significant activity of cisplatin in Walker 256 carcinoma; Dunning ascitic leukemia and P388 leukemia.

The major problem based on this drug is its high toxicity (Gershenson *et al.*, 1981). The haematological side effects of intraperitoneal administration of cisplatin include diminution of circulating reticulating reticuocytes, erythrocytes, leucocytes and platelets. Histologic studies revealed striking changes in the thymus, spleen and bone marrow depression (Rothman & Weich, 1981).

Preclinical, toxicologic evaluation of intravenous injection of cisplatin in dogs, monkeys and mice was submitted toxic signs included severe haemorrhagic enterocolitis, severe hypocellularity of bone marrow and lymphoid tissues (Kociba & Sleight, 1971).

Additional haematotoxicities of interest include the suppression of normal mechanisms promoting erythropoiesis such as erythropoietin hormone (Lechner *et al.*, 1992) ro glutathione peroxidase (Zang & Lindup, 1993).

Depletion of mitochondrial glutathione by cisplatin is an early and determinant event in the pathogenesis of cisplatin toxicity and mitochondria are suspectable to cisplatin-induced oxidative stress (Zhang & Lindup, 1993), on the other hand Glutathione peroxidase, is an integral component, provides a second line of defense against peroxidase before they can propagate in chain reactions, damaging membrane, and other cell components such as hemoglobin and erythrocytes (Harper *et al.*, 1979).

Several approaches have been used to prevent or improve cisplatin side effects. Such as manipulation of administration rate (Schaeppi *et al.*, 1973; Kishimoto *et al.*, 1989). Hydration and enforced duries (Goldberg, 1973; Rodney, 1995) and Chemotherapy (Ross & Gale, 1979; Deegan *et al.*, 1994).

In this perspective lasix is used because the protective effect of it against cisplatin is consistent with the studies of Goldberg (1973); Cvikovic *et al.* (1977), Hayes *et al.* (1977); Guarino *et al.* (1979) and El-Shazly *et al.* (1989). The concluded that the protection offered by furosemide (lasix) as due preliminary to resultant lower concentration of platinum in the urine or furosemide bound to plasma albumin and may complete for sites on the protein with this drug.

On the other hand, selenium is used because many investigators discussed the reasons of the protective effect of it on the toxicity of heavy metals and indicated that this could be attributed to the formation of a metal-selenium complex (Naganuma *et al.*, 1984; Baldew, 1990; Baldew *et al.*, 1991); or increasing of glutathione peroxidase biosynthetic pathway (Eaton *et al.*, 1980; Chung & Maines, 1982; Araya *et al.*, 1990); or enhancement of metallothionine synthesis in the liver and kidney (Xuzl *et al.*, 1994).

So present study was undertaken to compare the effect of lasix and selenium or both on the side effect of lasix and selenium or both on the side effects induced by the anticancer drug cisplatin on the haemopoietic system in the adult male rabbits.

Materials and Methods

Animals: New zealand white male rabbits (1000 ± 50g) were obtained from Abees farm. They were housed in groups in stainless cages, at room temperature of 22-25°C and photoperiod of 12h/d. They were acclimated for at least 10 days prior to experiment. They were permitted for free access to food (Purina Chow) and tap water. Animals were fasted 10 hrs before any experiment.

Chemical:

(a) Cisplatin was obtained from David Bull laboratories, Australia. Each ml contains 1 mg cisplatin.
(b) Lasix (4 choloro-N(-2-furylmethyl-5-sulfanoyl anthranilic acid) was obtained from Hoechst laboratories. Each ml contains 10 mg of furosemide.
(c) Sodium selenite ($Na_2SO_3^-5H_2O$) was obtainedfrom Merch Darmstadi. A stock solution (20 mol/ml) was obtained by dissolving the salt in sterile distilled water.

Experimental design: Table 1 summerizes the doses given to the animals. These doses were divided into 5 consecutive days and were repeated after 4 weeks of the initial dose.

Table 1: Dose and mode of cisplatin, lasix and sodium selenite administrations.

Group number	Treatment	Doses		
		Cisplatin	Lasix	Sodium Selenite
1	Control	-	-	-
2	Cisplatin	8 mg/kg	-	-
3	Lasix	-	0.25 mg/kg	-
4	Sodium Selenite	-	-	20 mol/kg
5	Cisplatin + Lasix	8 mg/kg	0.25 mg/kg	-
6	Cisplatin + Sodium	8 mg/kg	-	20 mol/kg
7	Cisplatin + Lasix + Sodium Selenite	8 mg/kg	0.25 mg/kg	20 mol/kg
	Mode of administration	i.p	i.m	i.m

Methods:

(I) Determination of the changes body weights and the percentage of changes in these weights;

The weights of six animals from each group, at the beginning of the experiment (Time zero), after five weeks of the initial injection were recorded.

The change in the body weight of animals was obtained by substracting the mean of the initial weight ($\bar{x}$-2) From the weight after one or five weeks of the first injection ($\bar{x}$-2)....

The percentage of change was calculated as follows:

$$\% \text{ change} = \frac{\bar{x}_2 - \bar{x}_1}{\bar{x}_1} \times 100$$

Preparation of blood and plasma: After one or five weeks of the initial drug administration, six rabbits were collected from each group, sacrified and the blood was collected into heparinized tubes. The heparinized blood samples were used for the determination of erythrocytic count, hemoglobin content, haematocrit value and leucocytic count. For plasma prepration, the blood was centrifuged and the supernatant plasma was used for bilirubin and iron levels. These parameters were determined according to the methods of

(1) Red blood cell counts (RBC's) (Wintrobe, 1967).
(2) Hemoglobin content (Hb) (Crosby *et al.*, 1954).
(3) Haematocrit value (Ht %) Oser 1979).
(4) Total leucocytic count (WBC's) (Miale, 1972).
(5) Bilirubin (Jendrassiki & Group, 1938).
(6) Iron level was determined by using Perkin-Elmer 2380 atomic absorption spectrophotometer.

Statistical analysis: Results were expressed as means of 6 experiments ± S. E. Data were analyzed by ANOV. If ANOVA indicated that there were significant ($P < 0.05$) differences among the seven groups, comparison were made using Duncan multiple range test (Wallenstein *et al.*, 1980).

Results

The data of the i.p injection of the therapeutic dose of cisplatin (8 mg/kg b. wt) alone or with lasix (0.25 mg/kg b. wt) or sodium selenite (20 μmol/kg b.wt) or cisplatin plus lasix plus sodium selenite on body weight and haematological parameter are illustrated in table (2-5). Cisplatin administration induced a marked decrease in body weight, it exhibited remarkable decreases in the number of red blood cells, hemoglobin contents, haematocrit values and white blood cell number. In addition to the elevations in the total bilirubin in the plasma and a decline in plasma iron levels. The coadministration of lasix (0.25 mg/kg b. wt) with cisplatin partially improved the loss of body weight and the treatment of haematological parameters. On the other hand sodium setenite (20 μmol/kg b.wt) with cisplatin completely improved the disturbances in tested haematological parameters, and partially preventing the loss of body weight. Coadministration of cisplatin plus lasix plus sodium selenite succeeded completely in preventing the haematological toxicities of cisplatin and the animals restored their normal weight again.

Discussion

Body weight: The results of the present investigation indicated that the administration of the therapeutic dose of cisplatin induced loss of body weight all over the experimental period. This loss may be due to diarrhoea or/and loss of appetite which were noticed during this study. Similar results were also recorded by other investigators. Schaeppi *et al.* (1973) stated that 5-daily injections of 2-5 mg/kg cisplatin caused anorexia, abdominal pain, haemorrhagic diarrhoea, dehydration and weight loss of monkeys.

Ward & Fauvie (1976) reported that 5-daily injections of five doses (0.5-12 mg/kg) of Cisplatin showed signs of weight decrease, diarrhoea and death of rats, from 2-7 days of the dose.

Daley-Yates & MC Brien (1984) found that the cisplatin treated groups had lost weight on day 6 after injection (-15 % compared to the control + 11 %)

Potkul *et al.* (1991) found a significant less weight gain during their study on cisplatin-treated rats (1 mg/kg) as compared with controls.

Sugiyama *et al.* (1995) reported that the intraperitoneal administration of 3.0 mg/kg cisplatin at times (3, 4, 5, 6, 7, 8, 01, 11 or 12 days) in dd mice inoculated with sarcoma 180 (S-180) cells caused decreases in food intake and body weight.

Haematological changes: Data obtained in this investigation indicated that the administration of the normal therapeutic dose of cisplatin (8 mg/kg body weight) divided on 5 consecutive days to rabbits and repeated after 4 weeks resulted in dramatic decreases in red blood cells count (RBC), hemoglobin contents (Hb) and haematocrit values (HT%). i.e. it caused severe anaemia after 7 days of administration. Also, the number of white blood cells decreased.

The present results support the previous observations in experimental animals as well as in humans. Rothman & Weich (1981) studies revealed decreases in circulating reticulocytes and lymphocytes of rats as a consequence of cisplatin administration at doses 1,2 or 3 mg/kg on 3 consecutive days or at 7.5 and 15 mg/kg as a single injection.

Schaeppi *et al.* (1973) indicated that administration of 5 daily injections of 0.31 and 0.16 mg/kg in monkeys led to anaemia, neutropenia and lymphopenia. Severe haemorrhagic enterocolitis, severe or moderate hypocellularity of the bone marrow, severe or marked hypocellularity of lymphoid tissues were noticed. Or 0.38 mg cisplatin/kg or one single dose of 2.5 mg cisplatin/kg exhibited anaemia neutropenia and lymphopenia.

In humans, Higby *et al.* (1973) Krakoff & Lippman (1974) and Wallace & Higby (1974), recorded transient moderate myelosuppression which appeared to be dose-related and possibly cumulative. The overall incidence of leukopenia and thrombocytopenia in 298 patients was 27 and 16 % respectively Doses of 50-60 mg/m^3 of cisplatin caus

Table 2: The effect of the i.p administration of the therapeutic dose of cisplatin (8 mg/kg b.wt. every weeks) with or without the im injection of the antidote (0.25 mg of Laces/kg b.wt or/and 20 μ mol of sodium selenite/kg b. wt.) As well as the antidote alone on the body weight and the percentages of the change in the bodies weights of male rabbit after one and five weeks of the initial drug administration

Group number	Treated group	Weeks after initial drug Administration				
		0	1		5	
		Mean ± S.E.b.wt.	% of Change	Mean ± S.E. b.wt	Mean ± S.E.b.wt	% of Change
1	Control	1000 ± 3.162	1150 ± 3.536	+15%	1250 ± 4.183	+25%
2	Cisplatin	1000 ± 4.183	820 ± 5.000[a]	-18 %	715 ± 3.873[a]	-28%
3	Lasix	1000 ± 2.739	1150 ± 2.236	+15%	1250 ± 4.744	+25
4	Sodium Selenite	1000 ± 3.160	1145 ± 5.000	+14.5	1240 ± 5.700	+24 %
5	Cisplatin + Lasix	1000 ± 2.236	1050 ± 5.477[ab]	+14%	1150 ± 6.519[a,b]	+20%
6	Cisplatin + Sodium Selenite	1000 ± 3.83	1080 ± 5.700[a,b]	+15 %	1165 ± 5.924[a,b]	+20.5 %
7	Cisplatin Lasix + So + d. Selenite	1000 ± 4.470	1155 ± 4.183[b]	+15 %	1250 ± 5.477[b]	+25 %

- Each value represents the mean of six experiments ± The standard error (g).
- a, b = Statistically significant ($P<0.05$) when compared with values of the control group or cisplatin treated group, respectively.

Table 3: The effect of the i.p. administration of the therapeutic dose of cisplatin (8 mg/kg b.wt every weeks) with or without the im injection of the antidote (0.25 mg of Lasix/kg b.wt or/and 20 μmol of sodium selenite /kg b.t) as well the antidote alone on the number of red blood cells (RBCs) and hemoglobin content in the blood of male rabbit after one and five weeks of the initial drug administration

Group number	Treated group (Erythrocytes counts; million/ml)	Weeks after initial drug Administration	
		1	5
1	Control	4.40 ± 0.28	4.41 ± 0.30
2	Cisplatin	3.90 ± 0.31	2.40 ± 0.36[a]
3	Laces	3.92 ± 0.31	4.39 ± 0.33
4	Sodium Selenite	4.62 ± 0.39	4.20 ± 0.46
5	Cisplatin + Lasix	4.60 ± 0.35	3.50 ± 0.21[a,b]
6	Cisplatin + Sodium Selenite	4.10 ± 0.42	4.40 ± 0.47[b]
7	Cisplatin + Lasix + Sodium Selenite	4.47 ± 0.19	4.52 ± 0.38[b]

Group number	Treated group (Hemoglobin content; g/dl)	Weeks after initial drug Administration	
		1	5
1	Control	11.80 ± 0.43	11.60 ± 0.45
2	Cisplatin	10.70 ± 0.47	6.60 ± 0.49[a]
3	Lasix	11.30 ± 0.40	11.10 ± 0.50
4	Sodium Selenite	12.10 ± 0.46	10.90 ± 0.44
5	Cisplatin + Lasix	12.10 ± 0.45	9.60 ± 0.49[a,b]
6	Cisplatin + Sodium Selenite	11.10 ± 0.38	11.80 ± 0.41[b]
7	Cisplatin + Laces + Sodium Selenite	12.20 ± 0.48	11.40 ± 0.50[b]

- Each value represents the mean of six experiments ± The standard error.
- a, b = Statistically significant ($P<0.05$) when compared with values of the control group or cisplatin treated group, respectively.

Table 4: The effect of the i.p. administration of the therapeutic dose of cisplatin (8 mg/kg b.wt every weeks) with or without the im injection of the antidote (0.25 mg of Lasix /kg b.wt or/and 20 μ mol of sodium selenite /kg b.wt.) as well the antidote alone on haematocrit value (HT) and the number of white blood cells (WBCs) in the blood of male rabbit after one and five weeks of the initial drug administration

Group number	Treated group (Haematocrit value)	Weeks after initial drug Administration	
		1	5
1	Control	33.50 ± 0.53	33.20 ± 0.47
2	Cisplatin	33.00 ± 0.43	22.00 ± 0.65[a]
3	Lasix	35.00 ± 0.59	34.00 ± 0.40
4	Sodium Selenite	34.20 ± 0.57	34.70 ± 0.51
5	Cisplatin + Laces	32.00 ± 0.45	29.00 ± 0.63[a,b]
6	Cisplatin + Sodium Selenite	31.80 ± 0.64	34.60 ± 0.49[b]
7	Cisplatin + Lasix + Sodium Selenite	33.40 ± 0.50	34.90 ± 0.64[b]

Group number	Treated group (Leucocyte counts; thousands/ml)	Weeks after initial drug administration	
		1	5
1	Control	4.90 ± 0.006	4.92 ± 0.003
2	Cisplatin	1.90 ± 0.032a	1.20 ± 0.16[a]
3	Lasix	4.85 ± 0.027	4.90 ± 0.024
4	Sodium Selenite	4.80 ± 0.070	4.90 ± 0.013
5	Cisplatin + Lasix	3.30 ± 0.100 a,b	3.00 ± 0.114[a,b]
6	Cisplatin + Sodium Selenite	4.80 ± 0.100b	4.90 ± 0.011[b]
7	Cisplatin + Lasix + Sodium Selenite	4.90 ± 0.015b	4.80 ± 0.055[b]

- Each value represents the mean of six experiments ± The standard error (thousands/ml)
- a, b = Statistically significant ($P<0.05$) when compared with values of the control group or cisplatin treated group, respectively.

decreases > 2.0 g/100 ml hemoglobin in 11 % of the patients. Leukopenia below 2000 Cells/mm3 or thrombocytopenia below 50,000 cells/mm3 rarely occurred (Wiltshaw & Kroner, 1976 and Yagoda *et al.*, 1976).

Cisplatin-induced myelosuppression (WBC < 2000/mm^3, platelets < 50,000 mm^3) was dos-related and occurred in approximately 25-30% of patients treated. The nadirs in circulating platelets and leukocytes occurred between days 18-23 after a dose of cisplatin (Prestayko *et al.*, 1979). Six of these patients required platelet transfusion.

Severe anaemia (haemoglobin < 8g/dl) occurred in 23% of 74 valuable patients, while 53% had haemoglobin < 10g/dl. Thrombocytopenia and/or granulocytopenia occurred in 69 % of evaluable course after 5-day continuous infusion of cis-DDP (Salem *et al.*, 1984).

Similarly Kociba & Sleight (1971) mentioned that a single intraperitioneal injection of a toxic dose of cis-diamminedichloro platinum (II) (12.2 mg/kg) in rats caused leukopenia, and depression in the number of circulating platelets, but it did not produce significant alterations in circulating erythrocytes, packed cell volume, and haemoglobin content. On the other hand the results of Newman *et al.* (1998) indicated that monkeys treated with 2.5 or 25 mg/kg cisplatin intravenously exhibited a decreases in red blood cell count, haemoglobin content, haematocrit value accompanied by an elevation in bilirubin levels.

In the light of the present data and work of previous investigators, it is reasonable to suppose that the anaemia reported in this work may be ascribed through (a) The suppression of normal mechanisms promoting erythropoiesis The work of Lechner *et al.* (1992) determined erythropoietin levels in 24 patients with different gynaecologic malignancies who were treated with cisplatin and endoxan. A statistically highly significant decrease was demonstrated 2h after starting

Table 5: The effect of the i.p. administration of the therapeutic dose of cisplatin (8 mg/kg b.wt every weeks) with or without the im injection of the antidote 30.25 mg of Lasix/kg b.wt. or/and 20 μmol of sodium selenite /kg b.wt) as well the antidote alone on the bilirubin and iron concentrations in the plasma of male rabbit after one and five weeks of the initial drug administration.

Group number	Treated group (Bilirubin contents ; mg/dl)	Weeks after initial drug Administration	
		1	5
1	Control	0.200±0.013	0.210± 0.016
2	Cisplatin	0.280±0.035	0.800±0.041[a]
3	Lasix	0.240±0.021	0.280±0.031
4	Sodium Selenite	0.270±0.038	0.260±0.024
5	Cisplatin + Lasix	0.280±0.033	0.520±0.020[a,b]
6	Cisplatin+Sodium Selenite	0.270±0.029	0.280±0.032[b]
7	Cisplatin+Lasix+Sodium Selenite	0.270±0.031	0.270±0.020[b]
Group Number	Treated group (Leucocyte counts; thousands/ml)	Weeks after initial drug administration	
		1	5
1	Control	54.0±1.225	54.0±1.304
2	Cisplatin	34.0±1.140[a]	30.0±.1.04[a]
3	Lasix	53.0±1.265	55.0±1.449
4	Sodium Selenite	52.0±1.000	51.0±1.378
5	Cisplatin+Lasix	48.0±0.758	47.0±0.791[a,b]
6	Cisplatin+Sodium Selenite	49.0±0.1.140[a,b]	48.0±0.949[a,b]
7	Cisplatin+Lasix+Sodium Selenite	55.0±1.265[b]	52.0±0.707[b]

- Each value represents the mean of six experiments ± The standard error (μg/dl)
- a, b = Statistically significant ($P<0.05$) when compared with values of the control group or cisplatin treated group, respectively.

treatment.

In the present study plasma iron concentrations decreased in response to cisplatin administration, the decrease in iron concentration which is necessary for haemoglobin synthesis may share to the reported anaemia.

The decreases in number of both red blood cells and white blood cells may also be due to inhibition in the mitotic activity of the bone marrow. Marrow failure is an important feature of acute leukaemias (Bunch, 1995). It is worthy to note that most cytotoxic drugs used in the trof malignant diseases exert their major effect on committed progenitors (Bunch, 1996).

(b) Shortened red cell life span: The results of the present study clearly shows increases in the total bilirubin response to cisplatin administration. Similar results, were obtained by other scientists. Pollera *et al.* (1987), Potkul *et al.* (1991) and Kyotani *et al.* (1993) who recorded increases in serum total bilirubin due to the treatment with cisplatin.

One of the most comment acquired reasons of anaemia is the shortening of red cell life span which can be due to abnormalities in the red cell membrane, the cytoplasmic enzyme system and/or in haemoglobin. These defects make the mature erythrocytes more susceptible to damage during their passage through the circulation and thus to the development of a haemolytic anaemia. Increased red-cell destruction release large quantities of haem into the cells of the reticulo endothelial system which is subsequently converted into bilirubin (Campbell *et al.*, 1984).

In addition to the inhibitory effect of cisplatin on the bone marrow (Newman *et al.*, 1998) which lead to the reduction in number of both RBCs and WBCs, Kociba & Sleight (1970) noticed reduction in the size of thymus gland and spleen. The abnormalities in their size may reflect the inability of these two organs to synthesize the WBCs.

The kidney infiltration of lymphocytes, which was observed in our previous study (Moussa *et al.*, 2000) and also recorded by Hardaker *et al.* (1974) and Reznik *et al.* (1993) may share in the noticed leukopenia.

The result of the present study indicated that co-administration of lasix with cisplatin partially improved the haematological side effects of the later, this is consistent with the results of Cvitkovic *et al.* (1977); Hayes *et al.* (1977); Merrin, 1976 & Merrin *et al.* (1978) who attributed this to that lasix may interact adversely with other drugs or bound to plasma albumin or complete for site on protein with cisplatin.

Ont the other hand, co-administration of sodium selenite with cisplatin completely improved the haematological side effect of this drug. The results of Naganuma *et al.* (1984) proved that selenium interact with platinum and alter its tissue distribution. Selenium has been shown to increase the concentrations of glutathione peroxidase. In erythrocytes haemoglobin and other tissues the enzyme glutathione peroxidase containing selenium as a prosthetic group which prevents the destruction of haemoglobin, erythrocytes and other tissues by peroxidase by forming reduced glutathione (Harper *et al.*, 1979 and Muray *et al.*, 1990). Xuzel *et al.* (1994) indicated that selenium increases the synthesis of metallothionein in the kidney and liver of rats.

So it can assumed that selenium may interact with the toxicity derived from platinum and modify its toxicity or it increases both the concentrations of glutathione peroxidase and metallothionein which may be involved in the protective effect of selenium against cisplatin haematotoxicity.

The prominent outcome of this study was that the simulatanous administration of lasix and sodium selenite together with cisplatin improved completely the haemotoxicity of cisplatin and the animals restored their normal weight.

So the results of the present data showing clinical improvement of cisplatin treated rabbits after treatment with lasix and selenium co-administration, which indicated the beneficial effect of this type of treatment, but additional work on the anticancer activity of cisplatin, when it is co-administrated with lasix and selenite is needed.

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