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EVALUATION OF ANTICANCER DRUG CISPLATIN ON SERUM HORMONE LEVELS OF THYROID GLAND IN MALE RAT (*RATTUS NORVEGICUS*)

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ABSTRACT:
Cancer can be develop in almost any organ or tissue, such as the lung, colon, breast, skin, bones or nerve tissue. The chemotherapeutic drugs Cisplatin ($C_{12}H_6N_2Pt$), the antineoplastic compounds in the class of alkylating agent used for the treatment of different kinds of cancer together with other chemotherapeutic agents. Toxic effect of Cisplatin on thyroid gland by evaluation of thyroid hormones (T_3 and T_4), pituitary hormone (TSH) were studied. The total body weights of all the animals treated with daily 2.5 and 5 mg/kg BW/ for 15 days with all the two drugs showed significant decrease in body weight ($P < 0.05$, $P < 0.001$). The total thyroid weight of all the animals treated with daily 2.5 and 5 mg/kg BW for15 days showed a significant increase in thyroid weight ($P < 0.05$, $P < 0.001$) as compared to control animals. A significant decrease in mean T_3 (triiodothyronine) and T_4 (Thyroxine) levels after Cisplatin, treatment is observed, however, with simultaneous significant increase in mean TSH (Thyroid stimulating hormone) levels, when compared to Vehicle-treated control. In the present study, it is observed that Cisplatin manifested more severe effects as evident by variability in the "types of cancers".
Key words: - *Anticancer drug, Serum hormones, Thyroid gland, Rat.*

INTRODUCTION:

Several anticancer drugs being used as chemotherapeutic agents for the treatment of cancer, during cancer treatment, the cancer cells are targeted and killed. But such treatments also kill good and healthy cells and this might cause enormous side effects on different body organs. Much work has been done to find out of these anticancer drugs in different body organs but little is known about its effects on target tissue particularly on thyroid gland. A perusal of literature has revealed that the platinum compounds, Cisplatin, exerts a number of side effects on the thyroid gland as well as on the Behavioral conditions, Ocular, Cutaneous and Dental (Adatia, 1975; Gonzalez et al. 2001; Mulvihill et al. 2003; Martin et al. 2005; Payne et al. 2005; Omoti and Omoti, 2006; Kamil et al. 2010; Sastry et al. 2012a; Sastry et al. 2012b; Sastry and Dighade, 2013; Goepfrich et al. 2013; Caiado et al. 2013; Ganash et al. 2014). However, there are no reports on thyroid gland with regard to Cisplatin, Carboplatin and Oxaliplatin hence it was felt essential and interesting to carry on the research work.

Amongst the various endocrine glands the only gland which has the unique activity of accumulating iodine in large quantities and converting it to organic bound form is "Thyroid". Enlargement of the gland during iodine deficiency demonstrates the importance of this essential micronutrient. The sole function of the thyroid gland is to secrete two important iodine containing hormones viz. triiodothyronine (T_3) and tetraiodothyronine or thyroxine (T_4). This hormones has an effect on nearly all tissues of the body where it increases cellular activity. The

formation of thyroid hormones is accomplished by the iodination of tyrosine residues of the protein, thyroglobulin. In all mammalian species, the thyroid hormones accelerate growth, enhance oxygen consumption, basal metabolic rate (BMR) and heat production, effect on growth, foetal and neonatal development. In pituitary, the hormones modulate the activity of thyrotrophs which in turn influence cell proliferation and growth of thyroid gland (Levitt, 1954; Williams and Bakke, 1962; Inzucchi et al. 1999; Greene et al. 2002; Barlas et al. 2002; Schlumberger and Pacini, 2006; Ain and Rosenthal, 2010; Liu et al. 2012; Tarino et al. 2013).

MATERIALS AND METHODS:

Experimental Animals-

For the present study sexually mature male Wistar rats weighing between 250 to 300 gms were selected. Maintenance and animal experimental procedure strictly followed "Principal of Laboratory Animal Care (NIH)"and also local"ethical regulations'.

Drugs and Chemicals-

The anticancer alkylating agent: Cisplatin manufactured by Oplax Marksans Pharma Limited, Mumbai (1mg/ml) were used for the present study.

Dose Preparation

The doses of the Cisplatin was decided on the basis of the LD50 values. Two different concentrations of drug was selected, 2.5mg and 5mg /KgBW daily for 15 days.

Experimental Protocols-

One week after arrival, male rats was administered Cisplatin drug (Oplax Marksans Pharma Ltd. India - 1mg/ml) intraperitoneally using one of the schedule according to protocols and control rats received equal amount of saline (Tables- 1 and 2).

Collection of Tissues-

Animals were sacrificed using chloroform 24hrs after the last day of each experiment. Immediately the thyroid gland were excised and cleaned from the adhering tissues then weighed.

Collection of Blood-

For the determination and evaluation of serum hormones T_3 (triiodothyronine), and T_4 (tetraiodothyronine or thyroxine) and TSH (Thyroid Stimulating Hormone) were made.

Parameters of Study was studied for-

In –Life Observation, Body Weight and Organ Weights.

Evaluation of Serum Hormones levels of T_3, T_4, TSH and T rats were determined.

Biostatistical Analysis-

The data was analysed statistically following the method adapted by Delgaard, 2008 and Standard Deviation (SD) and Student t-test were done by using Microsoft Excel to determine whether differences existed between the means were significant or insignificant, and results were considered significant at $P < 0.05$.

RESULT & DISCUSSION:

Toxic effects of anti-cancers drug, Cisplatin have been studied with respect to the following parameters using Cisplatin as 2.5 mg / Kg BW/ for 15 days and 5mg / Kg BW/ for 15 days in comparison with the Vehicle-treated rats with same doses and same durations.

Body Weight-

Body weight increases with age in the control rats but in treated animals body weight somewhat lowered during and after exposure to drug. There was a significant dose dependent decrease in the body weight of Cisplatin treated rats, however, vehicle-treated control tended to gain in the body weight because of saline administration.

Vehicle -treated Control-

The body weight ranged from 260.58 g to 272.13g in a mature rats used for the present study (Table-3 and fig.3).

- 2.5mg / Kg BW/ for 15 days Cisplatin treatment

The total body weights of all the animals treated with daily 2.5, showed significant decrease in body weight($P < 0.05$) (Table-3 and fig.3).

- 5mg / Kg BW/ for 15 days Cisplatin treatment

The total body weights of all the animals treated with daily 5 mg/kg BW/ for 15 days showedsliglity significant decrease in body weight ($P < 0.001$) when compared with 2.5 mg/Kg BW (Table-3 and fig.3).

Organ Weight (Thyroid)-

At the end of the treatment, we observed more or less increase in the weight of thyroid gland,

Vehicle -treated Control-

In the mature rat the weight of the thyroid gland ranged from 12.00±0.42 to18.66± 0.44 (Table-4 and fig.4).

- 2.5mg / Kg BW/ for 15 days Cisplatin treatment

The total thyroid weights of all the animals treated with daily 2.5 mg/kg BW/ for 15 days showed increase in thyroid weight ($P < 0.05$) when compared to control animals (Table- 4 and fig.4).

- 5mg / Kg BW/ for 15 days Cisplatin treatment

The total thyroid weights of all the animals treated with daily 5 mg/kg BW/ for 15 days showed increase in thyroid weight ($P < 0.001$), when compared to control animals (Table- 4 and fig. 4).

Evaluation of Serum Hormones-

Following hormones were evaluated and observed to see the effects in the thyroid gland for all the experimental groups.

T_3 (Triiodothyronine)

- **Vehicle-treated control**

The mean serum T_3 (triiodothyronine) levels of the vehicle-treated control and Cisplatin, treated rats are depicted in (Tables- 5 and Fig.5).

- **2.5mg/KgBW/day for 15 day**

The Cisplatin 2.5mg/KgBW daily for 15 days resulted into significant decrease in mean T_3 (triiodothyronine) levels (ng/dl) irrespective of variations in the concentrations and durations when compared to the Vehicle-treated control rats (Table- 5 and fig.5).

- **5mg/KgBW/day for 15 day**

The Cisplatin 5mg/KgBW daily for 15 days resulted into significant decrease in mean T_3 (triiodothyronine) levels (ng/dl) when compared to the 2.5 mg/KgBW and Vehicle-treated control rats (Table- 5 and fig.5).

T_4 (Thyroxine)

- **Vehicle-treated control**

The mean serum T_4 (Thyroxine) levels of the vehicle-treated control and Cisplatin treated rats are depicted in (Table-6 and figs.6).

- **2.5mg/KgBW/day for 15 day**

The Cisplatin 2.5mg/KgBW daily for 15 days resulted into significant decrease in mean T_4 (thyroxine) levels (ug/dl) irrespective of variations in the concentrations and durations when compared to the Vehicle-treated control rats (Table-6 and fig.6).

- **5mg/KgBW/day for 15 day**

The Cisplatin 5mg/KgBW daily for 15 days resulted into significant decrease in mean T_4 (thyroxine) levels (ug/dl) when compared to the 2.5 mg/KgBW as and Vehicle-treated control rats (Table-6 and fig.6).

TSH (Thyroid Stimulating Hormone)

- **Vehicle-treated control**

The mean serum TSH (Thyroid stimulating hormone) levels of the vehicle- treated control and Cisplatin treated rats are depicted in (Tables-7 and figs.7).

- **2.5mg/KgBW/day for 15 day**

The Cisplatin, dose regimens (2.5mg /KgBW) resulted into significant increase in mean TSH (Thyroid stimulating hormone) levels (mlU/ml) irrespective of variations in the concentrations and durations when compared to the Vehicle-treated control rats (Table-7 and fig.7).

- **5mg/KgBW/day for 15 day**

The Cisplatin, dose regimens (5mg /KgBW) resulted into significant increase in mean TSH (Thyroid stimulating hormone) levels (mlU/ml) irrespective of variations in the concentrations and durations when compared to the Vehicle-treated control rats and 2.5mg/Kg BW (Table-7 and fig.7).

Dealing with the side effects of chemotherapy has always been a major concern therefore the present work has put forth certain alterations to be discussed and utilized for the well-being of mankind.

In the present study the body weight was recorded before and after each treatment of anticancer drugs Cisplatin, (2.5, and 5, mg/Kg BW/day) for 15 days which resulted into a significant decrease in the body weight ($P< 0.0001$, $P <0.01$), From the foregoing it is concluded that present results are in accordance with the results of previous workers who noticed a decrease in the body weight. There was a significant increase in serum TSH levels with decrease in T_3 and T_4 proving thyroid hormones have a role in maintaining the body weight since it plays a crucial role in regulating differentiation, growth and metabolism in higher organisms by virtually affecting all organ system (Schwartz, 1983; Strait et al.1990)

However it is suggested that a reduction in the total body weight may be due to decline in the circulating blood serum androgen since androgen are a potent stimulant of nitrogen retention and their administration readily leads to an increase in body weight in both men and women (Forbes, 1985; Bhasin et al. 1997; Quarles van Ufford-Mannesse et al. 2005). Correlative to the above statement in the present study a decline in the circulating blood serum androgen have been noticed. Similarly androgen increases muscles mass therefore an increased serum concentration of potassium (Kupperman, 1971; Turner and Bagnara, 1976) which maintain body weight but this is not applicable to our present results.

The thyroid gland is a member of our endocrine system, it is one of the largest endocrine glands, produces thyroid hormones, the principal ones being triiodothyronine (T_3) and thyroxin which can sometimes be referred to as tetraiodothyronine (T_4). These hormones affect almost every cell in body, and help control growth and metabolism. Since no literature is available on the effect of the drugs Cisplatin, on thyroid weight, the present study has considered the effects of some other common drugs, antithyroid drugs and radioactive substances to which our results are more or less equivalent. In the weight of thyroid gland there was a significant increase after the administration of methylthiouracil (Philp et al. 1969). In the present study Cisplatin (2.5 and 5mg/kg BW/day) for 15 days resulted into a significant increase in the thyroid weight ($P< 0.0001$, $P < 0.002$). Therefore, it is concluded that our results are in accordance with the results of previous workers who noticed an increase in the thyroid weight.

Evaluation of Serum Hormones T_3 (Triiodothyronine), T_4 (Thyroxine) and TSH (Thyroid Stimulating hormone)-

Thyroid hormones are the only iodine-containing compounds with biological activity. Tri-iodo-thyronine (T_3) is the locally active form with one less iodine atom. It serves a variety of useful purposes around the body and is synthesized by modifying tyrosine moieties in a special glycoprotein (thyroglobulin) which is then stored in the thyroid gland and is available for hydrolysis as the hormone is needed. Thyroid hormone through its nuclear receptor, plays a crucial role in regulating differentiation, growth and metabolism in higher organisms. Thyroid receptors (TRs) and steroid hormone receptor share many properties, including ligand–dependant activation, nuclear site of action, sequence-specific DNA recognition sites and the ability to regulate gene transcription. Thyroxine (T_4) and triiodothyronine (T_3) are produced from

the thyroid gland. T_4 is produced only from the thyroid, whereas T_3 from the thyroid and from T_4 deiodination in extrathyroidal tissues.T_3 deficiency is responsible for the clinical and biochemical manifestations of hypothyroidism.

Perusal of the literature revealed that the levels of T_3 and T_4 were decreased, however, at the same time there was increase in serum TSH levels after amiodarone (Burger et al. 1976; Sogol et al.1983; Ceppi and Zaninovich, 1989; Newman et al. 1998; Loh, 2000; Bartalena et al. 1986; Harjai and Licata, 1997),chemotherapy and radiotherapy (Bartelena et al. 1986; Weissler and Berry, 1991; VanSanten et al. 2005), Phenobarbital and other antithyroid drugs (McClain, 1988; Barter and Klaassen, 1994; Scanlon and Toft, 1996; Hood et al.1999;Taurog, 2000; Cooper et al. 2006;Liu et al. 2012), methimazole, tapazole, PTU and MMI (Kitahori et al. 1984; Djurica et al. 1990; Van Seten and Moolenaar 1991; DeRuiter, 2002), acrylamide (Sharma and Jain, 2008), Glucocortcoids (Gamstedt et. al. 1981), 2,3,7,8-tetrachorodibenzo-p-dioxin (Nishimura et al. 2012),cyanide (Banerjee et al. 1997),UDP-glucuronosyltransferase (Barter and Klaassen, 1994), iodine dificiency (Ishi, 1983), phenyton, carbamazepine and rifampin (Smith and Surks, 1984),5'- monodeiodination (Harjai and Licata, 1997; Loh, 2000), napenopin (Kaiser et al. 1988), bexarotene (Torino et al. 2013). Because these drugs or chemicals have been inhibitedthe local conversion of T_4 to T_3 in the pituitary and hypothalamus, thereby decreasing the local amount of available T_3 and subsequently increasing significantly TSH secretion. Our results are in accordance with the above workers. It has been well established that TSH secretion by the pituitary is inversely related to thyroid hormone levels that serve as the basis for feedback control of circulating thyroid hormone. The synthesis of TSH protein subunits and TSH secretion are strongly suppressed by T_3 but are up regulated in the absence of T_3 (Williams, 1992). As such, increased levels of TSH are likely due to reduced thyroid hormone signal perceived by the pituitary gland. It is puzzling, therefore that TSH levels are elevated at doses of mixture well below those causing significant reduction in circulating T_4 (Wade et. al.2002). The general statement is that an increase in serum of TSH and decrease in serum T_3 and T4 concentrations are probably due to secretory capacity of thyrotroph cells of the pituitary, other possibility include increased T_3 transport into the thyrotroph cells and increased thyrotroph cell sensitivity to T_3 as a result of decreased TRH.

CONCLUSION:

- The total body weights of all the animals treated with daily 2.5 and 5 mg/kg BW/ for 15 days with all the two drugs showed significant decrease in body weight ($P < 0.05$, $P < 0.001$).
- The total thyroid weight of all the animals treated with daily 2.5 and 5 mg/kg BW for15 days showed a significant increase in thyroid weight ($P < 0.05$, $P < 0.001$) as compared to control animals.
- A significant decrease in mean T_3 (triiodothyronine) and T_4 (Thyroxine) levels after Cisplatin, however, with simultaneous significant increase in mean TSH (Thyroid stimulating hormone) levels, when compared to Vehicle-treated control.
- An increase in serum of TSH and decrease in serum T3 and T4 concentrations are probably due to secretary capacity of thyrotroph cells of the pituitary gland.

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Table -1: Experimental design for dose 2.5mg daily Cisplatin treatment

Number of animals and sex	Treatment	Dose mg/kg BW	Route	Duration
6 males (Experimental)	Cisplatin	2.5 mg daily	I.P.	15 days
6 males (Control)	Saline	E.V.	I.P.	S.D.

Table - 2: Experimental design for dose 5mg daily Cisplatin treatment

Number of animals and sex	Treatment	Dose mg/kg BW	Route	Duration
6 males (Experimental)	Cisplatin	5 mg daily	I.P.	15 days
6 males (Control)	Saline	E.V.	I.P.	S.D.

Abbreviations: E.V. = Equal Volume, S.D. = Same Durations, I.P. = Intraperitoneal, BW=Body Weight.

Table 3: Body weight variations in male rats treated with different concentration of Cisplatin

Treatment		Control	Cisplatin	
Dose (mg/KgBW) / Days		Saline (Equal Volume)	2.5mg (15 days)	5mg (15 days)
Total Body Weight (g)	Before treatment (Initial)	260.58± 0.23*	278.50± 0.76**	276.83±0.60*
	After treatment (Final)	272.13± 0.48*	270.0± 0.57*	265.66±0.44*

Values are mean ± SEM, n=6 in each group, *Significant at P< 0.05,** Highly Significant at P< 0.001.

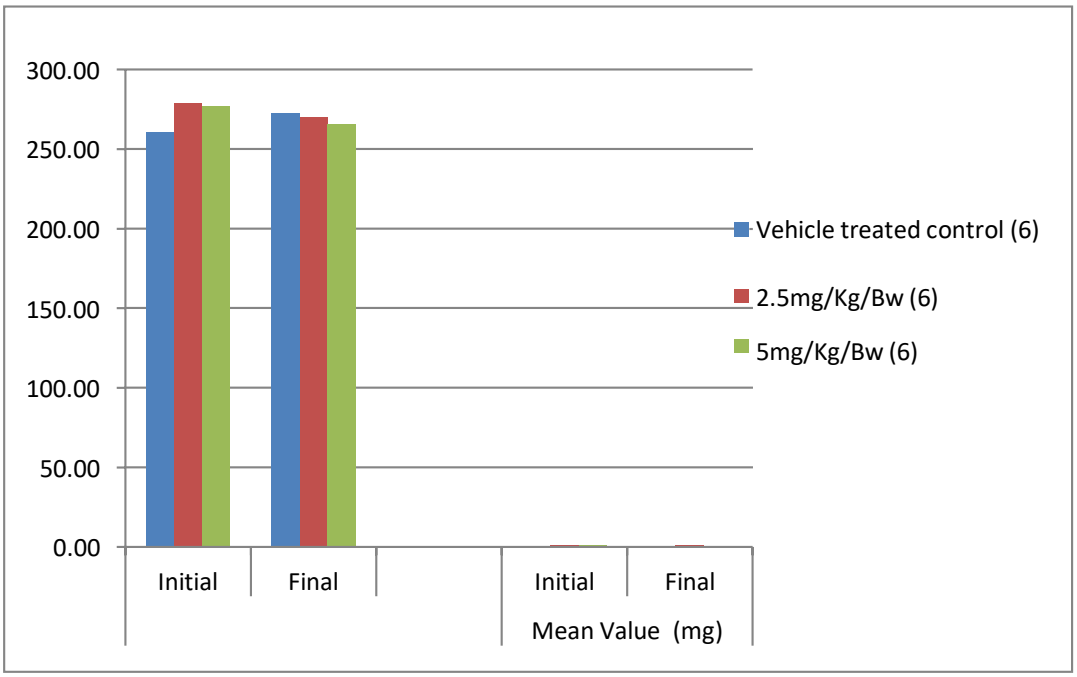

Fig. 3: Body weight variations in male rats treated with different concentration of Cisplatin

Table 4: Thyroid gland weights after Control and Cisplatin treatment

Treatment	Control	Cisplatin	
Dose (mg/KgBW) / Days	Saline(Equal Volume)	2.5mg(15days)	5mg(15 days)
Total Organ Weight / Thyroid weight (mg)	12.00±0.42*	16.00±0.57*	21.33±0.49*

Values are mean ± SEM, n=6 in each group, *Significant at P< 0.05, ** Highly Significant at P< 0.001.

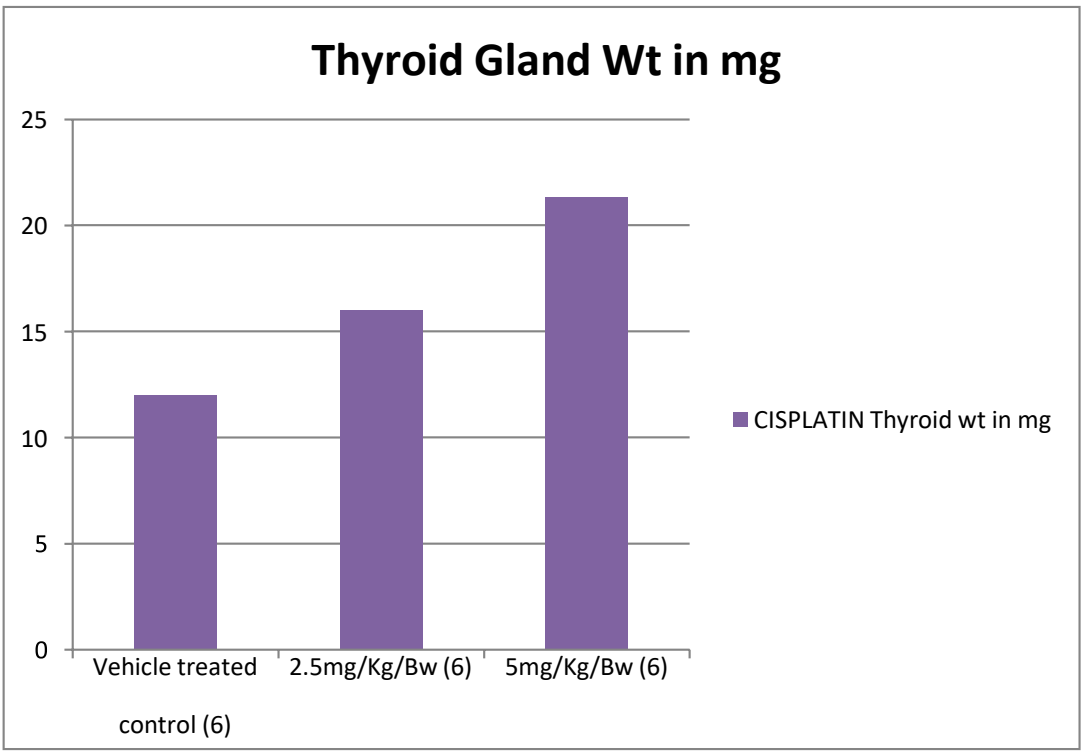

Fig. 4: Thyroid gland weights after Control and Cisplatin treatment

Table 5: Effect of Cisplatin on serum T_3 (Triiodothyronine) levels

Treatment	Control	Cisplatin	
Dose (mg/KgBW) / Days	Saline (Equal Volume)	2.5mg (30 days)	5mg (30 days)
Serum T_3(Triiodothyronine) levels (ng/dl)	57.72±0.28*	49.65±0.36*	47.86±0.34*

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Values are mean ± SEM, n=6 in each group, *Significant at P< 0.05,

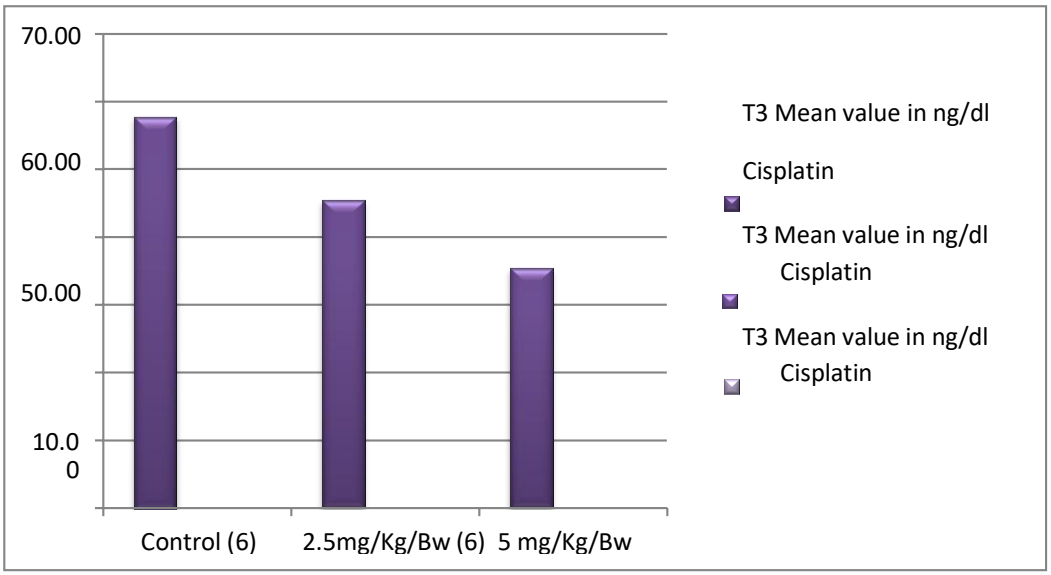

Fig 5: Effect of Cisplatin on serum T_3 (Triiodothyronine) levels

Treatment	Control	Cisplatin	
Dose (mg/KgBW) / Days	Saline (Equal Volume)	2.5mg (15 days)	5mg (15 days)
Serum T_4 (Thyroxine) levels (µg/ml)	5.31±0.003*	4.30±0.145*	3.34±0.02*

Values are mean ± SEM, n=6 in each group, *Significant at P< 0.05

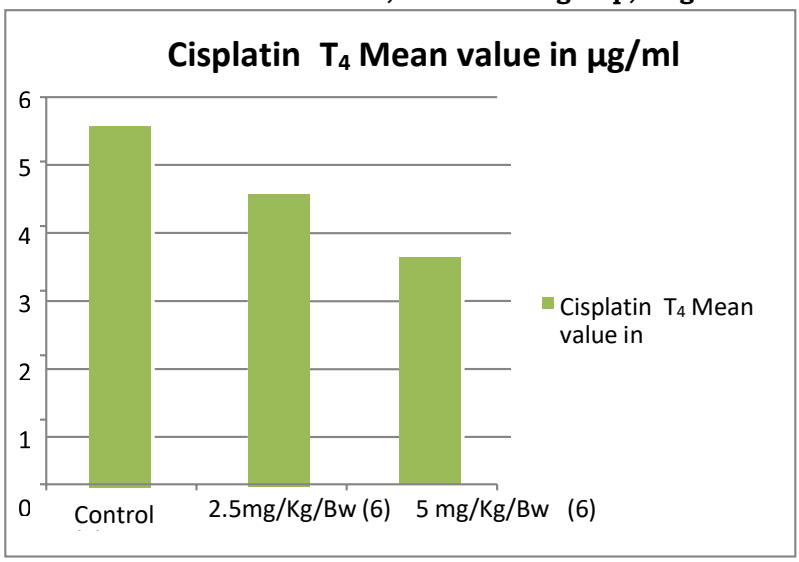

Fig. 6: Effect of Cisplatin treatment on the serum T_4 (Thyroxine) levels

Table 7: Effect of Cisplatin on the serum TSH (Thyroid stimulating hormone) levels

Treatment	Control	Cisplatin	
Dose (mg/KgBW) / Days	Saline (Equal Volume)	2.5mg (15 days)	5mg (15 days)
SerumTSHlevels (mIU/ml)	0.277± 0.0003*	0.292± 0.0003*	0.304±0.003*

Values are mean ± SEM, n=6 in each group, *Significant at P< 0.05.

Fig.7: Effect of Cisplatin on the serum TSH (Thyroid stimulating hormone) level