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Morphological Alterations after Platinum Analogue Cisplatin, Carboplatin and Oxaliplatin in the Male Albino Rat (*Rattus Norvegicus)*

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Abstract: *Antineoplastic chemotherapies are widely used in many therapeutic protocols and are responsible for numerous side effects. While studying the effects of platinum containing anticancer drugs or platinum analogues such as Cisplatin, Carboplatin and Oxaliplatin on the thyroid gland of rats some alterations in the behavioral parameters including diminished food and water consumption hence weight loss, sluggish and cachectic appearance, withdrawn mood, numbness of foot and arm were observed. Systemic anticancer therapies can produce acute and chronic organ damage, but the eye is usually considered a protected site since the ocular-visual system has high degree of sensitivity to toxic substances, the reported effects included blood red eyes, profuse bleeding from eyes, papilliedema, conjunctivitis, asymmetric retraction involved lower eyelid, lacrimation, excessive tearing, photophobia. These drugs also found to be responsible for numerous cutaneous and mucocutaneous side effects such as facial edema, swollen snout, blackening of incisor, hairs loss with alopecia, ruffled and brittle hairs. These side effects were dose and duration dependent and occurred in varying degree of frequency and severity with each drug, however, it was noted that these side effects were more prominent with Cisplatin, moderate with Carboplatin and less after Oxaliplatin treatments. Such studies would be useful to ophthalmologist, dermatologist, oncologist, and in clinical management of oncology patients.*

Keywords: *Antineoplastic chemotherapy, Cisplatin, Carboplatin, Oxaliplatin, Behavioral, Ocular, Cutaneous.*

1. INTRODUCTION

This article focuses on the behavioral, ocular and cutaneous side effects of some platinum analogues such as Cisplatin, Carboplatin and Oxaliplatin while studying their adverse effects on thyroid gland of rats. Such studies would definitely be useful to pharmacists, dermatologist and oncologist in the clinical management of oncology patients.

Cancer chemotherapy has the potential to produce acute and chronic damage in any organ system [10, 13, 18, 21, 22, 23, 25, 29, 30, 32].Similar to the above statement we observed a number of behavioral, morphological, ocular, cutaneous as well as dental side effects in the rat *Rattusnorvegicus* at dose levels of some platinum analogues (2.5, 5 and 15mg/KgBW for 15 days).

Some organs are more sensitive than others. In this context, the eye is usually considered a sanctuary site, but has a potentially high degree of sensitivity to toxic substances [3, 13, 19, 22, 25, 33, 35].

Chemotherapeutic agents generally target rapidly dividing cells and consequently are toxic to organ systems with high metabolic rates, such as hairs and skin [6, 9, 15, 34]. Much of our information on these cutaneous side effects comes from one decade study in this laboratory on various chemotherapeutic drugs while studying the adverse effect on thyroid gland.

Understanding such side effects will assist the ophthalmologist, dermatologist and oncologist to recognize them early and intervene before major problems occur. It is also essential to pharmacists involved in the clinical management of oncology patients.

2. MATERIALS AND METHODS

2.1. Drugs

Alkylating agent: Cisplatin, Carboplatin, Oxaliplatin, Drugs (1mg/ml) by Oplax Marksans Pharma Ltd. Mumbai (India) was used in present study.

2.2. Animals

For the present study healthy male Wistar strain albino rats weighing 281.67±6.01-276.00±3.06g were obtained from the breeding colony of Department of Biochemistry, RTM Nagpur University, Nagpur, and were raised on a commercial pellet diet (Hindustan lever Ltd.) and water *ad libitum*. The animals were housed at constant temperature (28±2ºC) and relative humidity (60±10%) with a 12h light: 12h dark cycle.

2.3. Treatments

Five sets of experiments were performed for each drug and compared with the vehicle-treated control. The drug was administered intraperitoneally. The doses used are summarized in Table-1.

Table1. *Experimental design*

Number of animals and sex	Treatment	Dose mg/Kg BW	Route	Duration
6 males (Experimental)	Cisplatin Carboplatin Oxaliplatin	2.5 mg daily	I.P.	15 days
6 males (Experimental)	Cisplatin Carboplatin Oxaliplatin	5 mg daily	I.P.	15 days
6 males (Experimental)	Cisplatin Carboplatin Oxaliplatin	10 mg (Once in a week)	I.P.	7 days
6 males (Experimental)	Cisplatin Carboplatin Oxaliplatin	15 mg daily	I.P.	15 days
6 males (Control)	Saline	E.V.	I.P.	Same Duration

Abbreviations: I.P. =Intraperitoneally, B.W. = Body weight, E.V. =Equal volume

3. RESULTS

Some of the side effects observed after Cisplatin, Carboplatin and Oxaliplatin with (2.5, 5 and 15 mg/KgBW daily for 15 days and 10 mg/KgBW once in a week for 7 days are summarized in Table-2. These reactions occurred in varying degrees of frequency and severity with each platinum containing anti-cancer compounds. On necropsy majority of the animals showed mottling/congestion/focal emphysema in liver and in lungs. Other vital organs such as kidney and brain did not show any gross lesion of pathological significance.

Table2. *Behavioral, Ocular, Cutaneous/ Mucocutaneous side effects of Cisplatin, Carboplatin and Oxaliplatin are summarized below.*

Drug	Dose & Duration	Behavioral	Ocular	Cutaneous/Mucocutaneous
Cisplatin	**2.5 (mg/KgBW for 15 days)**	▪ Diminished food and water consumption hence weight loss sluggish appearance.	▪ None	▪ Facial edema ▪ Partial alopecia from dorsal side
	5 (mg/KgBW for 15 days)	▪ Noticeable Weight loss & weakness	▪ Blood red eyes ▪ Epsilateral haemorrhage ▪ Protrusion of the eyes ▪Conjunctivitis	▪ Swollen snout ▪ Blackening of incisor
	10 (mg/KgBW for once in a week for 7 days)	▪ None	▪ None	▪ None
	15 (mg/KgBW for 15 days)	▪ Weight loss. ▪ Weakness. ▪ Numbness of foot and arm. ▪ Irreversible foot and arm due to softening of bone. ▪ Reduced Limb movement.	▪ Asymmetric retraction involved lower eyelid, hence excessive eyelid dermatitis. ▪ Profuse	▪ Excessive Swelling of snout. ▪ Ruffled hairs ▪ Skin adnexes especially hairs loss with alopecia prominent on lateral side. ▪ Brittled and ruffled hairs. ▪ Wound formation

			Bleeding from eyes. ▪ Protrusion of the eyes with Papilliedema. ▪ Haemorrhage ▪ Excess Enlargement of the extraocular Muscle edema. ▪ Protrusion of the eyes with papilliedema ▪ Decreased visual acuity. ▪ Excessive tearing. ▪ Photophobia.	▪Hypersentivity
Carboplatin	**2.5 (mg/KgBW for 15 days**	▪ Shivering. ▪ Diminished food and water consumption.	▪ Lacrimation. ▪ Inflammation.	▪Partial hair loss with alopecia. ▪ Skin irritation.
	5 (mg/KgBW for 15 days)	▪ Shivering. ▪ Difficulty in breathing ▪Sluggish appearance.	▪Visual disturbances.	▪ Brittleness and ruffleness of hairs. ▪ Red streaks along injection site.
	10 (mg/KgBW for once in a week for 7 days)	▪ None	▪ None	▪ None
	15 (mg/KgBW for 15 days)	▪ Weakness. ▪ Diarrhea. ▪ Weight loss. ▪ Decreased locomotor activity. ▪ Breathlessness. ▪ Oligourea.	▪ Less haemorrhage. ▪ Less Protrusion of the eye (Proptosis). ▪ Asymmetric Eyelid retraction. ▪ Enlargement of the extraocular muscle edema. ▪ Blurring of vision ▪ Photophobia ▪ Tearing.	▪ Hair loss from dorsal and lateral side. ▪ Less swelling on snout. ▪ Soft reddish Excreta. ▪ Less swelling on snout. ▪ Sparsness of the hairs on snout. ▪ Sparsness of the hairs hence partial alopecia. ▪ Erythema (Redness of the skin) ▪ Hypersentivity
Oxaliplatin	**2.5 (mg/KgBW for 15 days)**	▪ Diminished food and water consumption hence sluggish appearance.	▪ Inflammation of eyes ▪Visual disturbances.	▪ Itching. ▪ Pain/redness/swelling at injection site.
	5 (mg/KgBW for 15 days)	▪ Unusual decrease in the amount of urine with pink/bloody Urine. ▪ Change in fecal matter (excreta) reddish and soft	▪ Less haemorrhage. ▪ Less Circum orbital edema or puffiness. ▪ Less Protrusion of eyes.	▪ Less Swelling and redness of snout.
	10 (mg/KgBW for once in a week for 7 days)	▪ None	▪ None	▪ None
	15 (mg/KgBW for 15 days)	▪ Weight loss. ▪ Decreased locomotor activity.	▪ Less haemor-rhage. ▪ Less Circum-orbital edema. ▪ Less protrution of eyes, the protruded eyes appear bloody red. ▪ Papilliedema ▪ Visual disturbances.	▪ Peculiarity retracted snout with reduced in length. ▪ Partial alopecia. ▪ Snout swollen and reddened ▪ Nostrils swollen and reddened. ▪ Alopecia, particularly on lateral side, hairs appear brittle ▪Hypersensitivity.

4. DISCUSSION

The behavioral alterations observed in the present study with platinum compounds is in conformity with the earlier literature on a number of antineoplastic drugs as well as heavy metals [27, 29, 30, 32].

The data from this report also provide sufficient evidence to relate ocular toxicity to the findings of earlier workers on platinum compounds [3, 8, 10, 11, 20, 21, 26, 28, 35]. From the foregoing it is concluded that the mechanism of visual toxicity induced by anti-neoplastic is unknown but may result from central nervous system accumulation of drug after repeated doses [3, 22, 33].

Similarly the cutaneous or dermatological complications of cancer chemotherapy have become an increasingly significant subject [5, 9, 12, 14, 15, 23]. Alopecia was the commonest effect observed with all these three drugs and also consistent to other studies [2, 6, 9, 15].The dermatological side effects concerned with hyperpigmentation was prevalent and specific to the all the drugs used in the present study as described in the literature by [15, 36].However, it was confined to nails in Carboplatin and Oxaliplatin[7, 34] .

Allergic skin reactions such as pruritus, purpura, rashes, itching, edema, phelebitis, erythema, injection site reaction (Pain/redness/swelling), skin irritation which varied in their symptoms depending upon the quantity of drug, such allergic skin reactions have been described by [4,14,37]. Similarly in the present study hypersentivity reactions were most commonly caused by platinum compounds were in accordance with observation of [6, 14, 24, 31]. Hyperpigmentation (dark coffee colour) of nails have been observed with Cisplatin, Nitrogen mustards, Cyclophosphamide and Doxorubicin [2, 9, 16, 23, 36]. Similarly nail changes were observed with other drugs such as Docetaxel. Blackening of incisor after high dose Cisplatin treatment is correlative to Cyclophosphmide[1, 17] .

From the foregoing it is concluded the oncologist, dermatologist, ophthalmologist, dentist and pharmacists need to be aware of the possibility of all such complication in order to develop intervention strategies that would minimize or eliminate an expected side effect.

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