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Research Paper

Effects of Platinum Containing Anticancer Drugs Cisplatin, Carboplatin Aand Oxaliplatin on Behavioral Parameters in the Male Albino Rat *(Rattus Norvegicus)*

Zoology

KEYWORDS : Antineoplastic chemotherapy, Cisplatin, Carboplatin, Oxaliplatin

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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 such as Cisplatin, Carboplatin and Oxaliplatin on the reproductive system and thyroid gland of rats, some alterations in the behavioral parameters including locomotory, ocular, cutaneous, dental etc. were noticed with the low chronic doses (2.5mg/KgBW) and high chronic doses (15mg/KgBW). Such studies would be useful to ophthalmologist, dermatologist, and oncologist and in clinical management of oncology patients.

INTRODUCTION

Cancer chemotherapy has the potential to produce acute and chronic damage in any organ system (Gonzalez et al. 2001; Mulvihill et al. 2003; Payne et al. 2005; Omoti and Omoti et al. 2006; Rodriguez et al. 2010). Similar to the above statement we observed a number of behavioral, morphological, ocular, cutaneous as well as dental side effects in the rat *Rattus norvegicus* with platinum containing antineoplastic agents such as Cisplatin, Carboplatin and Oxaliplatin at dose levels of (2.5mg/KgBW and 15mg/KgBW). Such studies would definitely be useful to pharmacists, dermatologist and oncologist in the clinical management of oncology patients (Peters, 1994; Jean McCann, 2000; Rodriguez et al. 2001).

MATERIALS AND METHODS

Drugs

Alkylating agents : Cisplatin, Carboplatin, Oxaliplatin, Drugs by Oplax Marksans Pharma Ltd. (1mg/ml).

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.

Treatments

Two 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.

Table 1: 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	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

RESULTS

Some of the side effects observed with two doses of all three drugs 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.

Table 2: Summary of side effects

Treatment	Behavioral	Ocular	Cutaneous/Mucocutaneous
Cisplatin (2.5mg/KgBW)	• Diminished food and water consumption • Shivering • Sluggish appearance	• Conjunctivitis • Asymmetric eyelid retraction involving both the eyelids • Periorbital puffiness	• Facial edema • Dryness and Redness of the skin (Erythema) • Hypersensitivity • Alopecia but prominent on dorsal side
Cisplatin (15mg/KgBW)	• Weight loss • Cachectic appearance • Weakness • Diarrhea • Seizures • Reduced limb movement • Numbness in foot and arm • Irreversible foot and arm due to softening of bone • Unusual decrease in the amount of urine with pink/bloody urine • 30% Mortality	• Conjunctivitis • Enlargement of the extraocular muscle edema / excessive periorbital adema • Haemorrhage • Protrusion of the eyes (Proptosis) • Visual disturbances • Bilateral papilledema • Photophobia • Excessive tearing • Eyelid dermatitis	• Skin adnexes especially with alopecia but prominent on lateral side • Localized hyperpigmentation • Puritus or allergic reaction • Hypersensitivity • Wound formation/skin necrosis • Brittleness and ruffleness of hairs • Red streaks along injection site • Nail loss • Hyperpigmentation of nails (dark coffee colour) • Blackening of incisor
Carboplatin (2.5mg/KgBW)	• Diminished food and water consumption • Sluggish appearance • Bizarre behavior	• Conjunctivitis • Protrusion of eyes	• Facial edema • Partial alopecia • Phelebitis • Skin irritation • Erythema (Redness of the skin) • Hyperpigmentation

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Carboplatin (15mg/KgBW)	• Shivering • Difficulty in breathing • Sweating • Decreased locomotor activity	• Conjunctivitis • Asymmetric eyelid retraction • Haemorrhage • Photophobia • Excessive tearing • Eyelid dermatitis	• Snout swelling • Sparsness of the hair • Nasal irritation • Hyperpigmentation of nails
Oxaliplatin (2.5mg/KgBW)	• Diminished food and water consumption • Sluggish movements	• Lacrimation • Inflammation • Eyelid dermatitis	• Partial alopecia • Puritus • Itching • Hyperpigmentation • Pain/redness/swelling of injection site
Oxaliplatin (15mg/KgBW)	• Weight loss • Decreased locomotor activity • Breathlessness • Oligourea	• Conjunctivitis • Asymmetric eyelid retraction • Haemorrhage • Lacrimation • Circumorbital edema • Visual disturbances	• Redness of the face • Partial alopecia • Hypersensitivity • Itching • Skin irritation • Figurated hyperpigmentation of skin • Skin peeling at some places • Injection site reaction (Pain/redness/swelling) • Hyperpigmentation of nails (dark coffee colour)

DISCUSSION

The behavioral alterations observed in the present study with platinum compounds is in conformity with the earlier literature on a number of heavy metals such as Sodium arsenite and Mercury (Rodriguez et al. 2001; Ramalingam et al. 2006; Rodriguez et al. 2010).

The data from this report also provide sufficient evidence to relate ocular toxicity to the findings of earlier workers on platinum compounds (Pippitt et al.1981; Curtis and Murtagh, 1993; Rankin and pitts, 1993; al-Tweigeri et al.1996; Hilliard et al.1997; Yang et al. 2000; Gonzalez et al. 2001; Mulvihill et al. 2003; Martin et al. 2005). From the foregoing it is inferred 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 (al-Tweigeri et al.1996; Omoti and Omoti et al.2006).

Similarly the cutaneous or dermatological complications of cancer chemotherapy have become an increasingly significant subject (Bronner and Hood, 1983; Hood, 1996; Fischer et al.1997; Payne et al. 2005; Kamil et al. 2008; Kamil et al. 2010). Alopecia was the commonest effect observed with all these three drugs and also consistent to other studies (Fischer et al.1997; Alley et al. 2002; Chandha and Shenoi, 2004; Kamil et al.2010). The dermatological side effects concerned with hyperpigmentation was prevalent and specific to all drugs used in the present study as described in the literature by Susser et al. 1999 and Kamil et al. 2010. Hyperpigmentation of the skin and nails (dark coffee colour of nails) have been observed with high doses of Cisplatin, Carboplatin, Oxaliplatin in the present study which has also been described by Fischer et al. 1997; Susser et al.1999; Correia et al.1999; Alley et al. 2002; Payne et al. 2005 with Nitrogen mustards, Cyclophosphamide and Doxorubicin. Allergic skin reactions such as pruritus, purpura, rashes, itching, edema, phlebitis, erythema, injection site reaction (Pain/redness/swelling), skin irritation which varied in their symptoms depending upon the quantity of drug, have been described by Trojan, 2002; Branzan et al. 2005; Kamil et al. 2008. Similarly hypersentivity reactions were in accordance with observations of Chandha and Shenoi, 2004; Rossi et al. 2004; Pejsa, 2004; Kamil et al. 2008. Similarly nail changes were correlative with other drugs such as Docetaxel, Taxanes and Anthracyclines (Gilbat et al.2009; Halvorson et al.2010; Ferreira et al.2010). Blackening of incisor after high dose Cisplatin treatment is correlative to Cyclophosphmide (Adatia,1975; Kaszuba et al. 2006).

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

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