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COMPARATIVE STUDY OF DAPSONE AND CYCLOPHOSPHAMIDE ON TREATMENT OF PAPILLOMA SKIN CANCER

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Abstract: In the present study, anti-cancer property of Dapsone was evaluated against 7, 12-dimethyl benz(a)anthracene (DMBA) induced skin tumorigenesis in Swiss albino mice. A single topical application of 7,12-dimethyl benz(a)anthracene (100 µg/100 µl of acetone), followed 2 weeks later by repeated application of croton oil (1% in acetone two times a week) for 8 weeks exhibited 100 percent tumor incidence (group IV). In contrast, animals treated orally with Dapsone (group V) and Cyclophosphamide (group VI) exhibited 40, 50 per cent tumor incidence, which significantly higher than 100% tumor incidence in the group IV (control). The cumulative number of papillomas during the observation period of 8 weeks was significantly decreased in the groups V and VI in compare to 25 cumulative numbers of papillomas in carcinogen control group. The tumor burden and tumor yield of V and VI group was significantly lesser (1.89, 2.9 and 1.82, 2.7) as compared to DMBA/ croton oil treated control (3.8 and 3.8). The study has revealed the inhibition of dimethylebenz (a) anthracene (DMBA)/croton oil induced skin tumorigenesis in Swiss albino mice by Dapsone treatment comparison to Cyclophosphamide.

Keywords: Chemoprevention, Dapsone, Cyclophosphamide, DMBA, Skin papillomagnesis

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INTRODUCTION

In the UK in 2010, 12, 818 people were diagnosed with malignant melanoma, and about 100,000 people were diagnosed with non-melanoma skin cancer. There were 2,746 deaths from skin cancer, 2,203 from malignant melanoma and 546 from non-malignant melanoma. In the US in 2008, 59,695 people were diagnosed with melanoma, and 8,623 people died from it[1]. Skin cancers (skin neoplasm) are named after the type of skin cell from which they arise. Basal cell cancer originates from the lowest layer of the epidermis, and is the most common but least dangerous skin cancer. Squamous cell cancer originates from the middle layer, and is less common but more likely to spread and, if untreated, become fatal. Melanoma, which originates in the pigment-producing cells (melanocytes), is the least common, but most aggressive, most likely to spread and, if untreated, become fatal[2]. Still, melanoma has one of the higher survival rates among major cancer, with over 75% of patients surviving 10 years in the UK during 2005-2007. There are three main types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma. There are a variety of different skin cancer symptoms. These include changes in the skin that do not heal, ulcering in the skin, discolored skin, and changes in existing moles, such as jagged edges to the mole and enlargement of the mole. Papilloma refers to a benign epithelial tumor growing exophytically (outwardly projecting) in finger-like fronds. In this context papilla refers to the projection created by the tumor, not a tumor on an already existing papilla (such as the nipple). When used without context, it frequently refers to infections (squamous cell papilloma) caused by human papillomavirus (HPV), such as warts. Papillomaviridae is an ancient taxonomic family of non-enveloped DNA viruses, collectively known as *papillomaviruses*. Several hundred species of papillomaviruses, traditionally referred to as "types", have been identified infecting all carefully inspected mammals[3], but also other amniotes such as birds, snakes and turtles[4, 5, 6]. Infection by most papillomavirus types, depending on the type, is either asymptomatic (e.g. most Beta-PVs) or causes small benign tumors, known as papillomas or warts (e.g. human papillomavirus1, HPV6 or HPV11). Papillomas caused by some types, however, such as human papillomaviruses 16 and 18, carry a risk of becoming cancerous[7]. Papillomaviruses are usually considered as highly host- and tissue-tropic, and are thought to rarely be transmitted between species[3]. Papillomaviruses replicate exclusively in the basal layer of the body surface tissues. All known papillomavirus types infect a particular body surface[8], typically the skin or mucosal epithelium of the genitals, anus, mouth, or airways. For example, human papillomavirus (HPV) type 1 tends to infect the soles of the feet, and

HPV type 2 the palms of the hands, where they may cause warts. Additionally, there are descriptions of the presence papillomavirus DNA in the blood and in the peripheral blood mononuclear cells[9]. Dapsone (diamino-diphenyl sulfone) is an antibacterial most commonly used in combination
with rifampicin and clofazimine as multidrug therapy (MDT) for the treatment of *Mycobacterium leprae* infections (leprosy). It is also second-line treatment for prophylaxis (prevention) against Pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii* (formerly *P. carinii*) in HIV patients in whom CD4 counts are below 200/mm^3 [10]. Dapsone is an odorless white to creamy-white crystalline powder with a slightly bitter taste, used in combination with pyrimethamine in the treatment of malaria[11, 12]. Dapsone is commercially available in both topical and oral formulations. Dapsone has anti-inflammatory and immunomodulatory effects[13], which are thought to come from the drug's blockade of myeloperoxidase. This is thought to be its mechanism of action in treating dermatitis herpetiformis[14].

Cyclophosphamide also known as cytophosphane is a nitrogen mustard alkylating agent, from the oxazophorines group[15]. It is used to treat cancers and autoimmune disorders. A prodrug, it is converted in the liver to active forms that have chemotherapeutic activity. Cyclophosphamide has severe and life-threatening adverse effects, including acute myeloid leukemia, bladder cancer, and permanent infertility, especially at higher doses. For autoimmune diseases, doctors often substitute less-toxic methotrexate or azathioprineafter an acute crisis[2]. The main use of cyclophosphamide is with other chemotherapy agents in the treatment of lymphomas, some forms of brain cancer, leukemia[16] and some solid tumors[17]. It is a chemotherapy drug that works by inducing the death of certain T cells. Adverse drug reactions include chemotherapy-induced nausea and vomiting, bone marrow suppression, stomachache, hemorrhagic cystitis, diarrhea, darkening of the skin/nails, alopecia (hair loss) or thinning of hair, changes in color and texture of the hair, and lethargy. Hemorrhagic cystitis is a frequent complication, but this is prevented by adequate fluid intake and mesna (sodium 2-mercaptoethane sulfonate), a sulfhydryl donor which binds acrolein. The present study was depending upon the search of less toxic and more effective drug.

MATERIALS AND METHODS

Animals:

Adult 7-8 weeks old male Swiss albino mice weighing 24±2 g were used for conducting this study. Four animals were housed in one polypropylene plastic cage containing saw

dust (procured locally) as bedding material. They were maintained under control conditions of temperature (25±2°c) and light (14 light: 10 dark). The animals were provided standard mice feed, procured from Sir Madanlal Institute of Pharmacy, Etawah, Uttar Pradesh (India), and water ad libitum. As a precaution against infections, tetracycline water was given to animals once in fortnight. Three days before the commencement of experiment, hair on the back of the mice were clipped in 3 X 3 cm^2 area. Only those mice showing no hair growth were used for the present study.

Chemicals:

Initiator, 7, 12 – Dimethylbenz (a) anthracene (DMBA) and promoter (Croton oil) were procured from Sigma Chemical o., St. Louis, USA.

Experimental design:

Skin of 3 X 3 cm^2 back area of animals was shaven three days before the commencement of experiment, and only those animals in the resting phase of hair cycle were selected for the study. A total of 60 selected animals were randomly divided into six groups (I, II, III, IV, V & VI) to evaluate chemopreventive role of Dapsone and Cyclophosphamide against DMBA/ croton oil induced skin papillomagenesis.

Group I-Vehicle control: 100 µl Acetone 2 times /week up to 8 weeks.

Group II- A single dose of DMBA (100g / 100l of acetone) over 3 X 3 cm^2 shaven area of the mice skin.

Group III-Croton Oil Alone: 1 % Croton oil was applied on skin 2 times a week up to 8 week.

Group IV-DMBA + Croton Oil: - 100g DMBA was dissolved in 100l acetone and single application was given afterwards 1 % Croton oil was applied on skin 2 times a week up to 8 week.

Group V-DMBA + Dapsone+ Croton oil: 100g DMBA was dissolved in 100l acetone and single application was given afterwards the 100 µl dose of Dapsone at the dose of 250 mg/kg b. wt. dose was given one hour before the each application of 1 % croton oil 2 times a week up to 8 weeks.

Group VI-DMBA + Cyclophosphamide + Croton oil: 100g DMBA was dissolved in 100l acetone and single application was given afterwards the Cyclophosphamide at the dose of 40 mg/kg b. wt. dose was given one hour before the each application of 1 % croton oil 2 times a week up to 8 weeks.

The following parameters were taken into consideration:

Body weight: Change in mean body weight was measured weekly. Tumor incidence: The number of mice carrying at least one tumor expressed as percent incidence. Cumulative number of papillomas: Total number of tumors bearing mice. Tumor yield: The average number of papillomas

per mouse. Tumor burden: The average number of tumors per tumor bearing mouse.

Statistical Analysis:

The results are expressed as the mean standard error of the mean or as a percentage.

RESULTS AND DISCUSSION

The body weight, tumor incidence, and the Cumulative numbers of papillomas per effective animal at week 8 after DMBA+ Croton oil initiations are shown in Table 1. The incidence of tumors after application of 250 mg/kg b. wt. of Dapsone and 40 mg/kg b. wt. of Cyclophosphamide to DMBA+ Croton oil initiated mice was reduced from 40 and 50% respectively. The numbers of Cumulative tumors per effective mouse in DMBA/Dapsone/ Croton oil and DMBA/Cyclophosphamide/ Croton oil groups are 14 and 17, respectively. Tumors were not observed in the vehicle controls. In DMBA/Croton oil group, all mouse developed a papillomas. These results are presented in Fig. 1.

In the present study, we show that effect of Dapsone on DMBA+Croton oil induced skin papillomas in mice and also compare with the standard drug Cyclophosphamide. The present data indicate that both Dapsone and Cyclophosphamide Showed protective effect against DMBA+Croton oil induced skin papillomas in mice. Dapsone significantly affects skin papillomas in mice in comparison to Cyclophosphamide. In this study we aimed to evaluate anti-tumor effect of Dapsone because it has mechanism of action in treating dermatitis herpetiformis and showed less adverse effect than Cyclophosphamide.

CONCLUSIONS

In the present research work comparative study of Dapsone and Cyclophosphamide in treatment Papilloma skin cancer on mice was carried out. The results showed that Dapsone is significantly more effective on papilloma skin cancer compare to Cyclophosphamide.

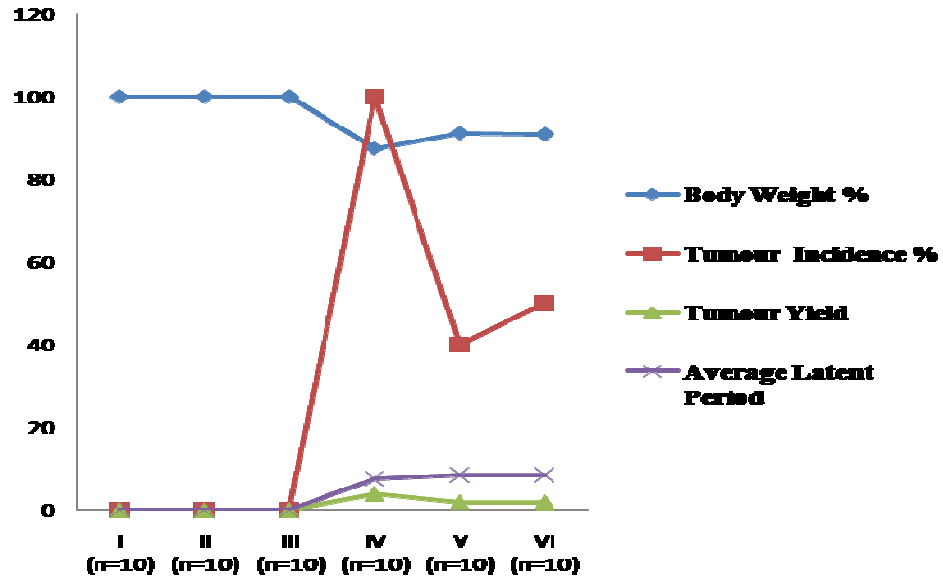

Figure 1 Effect of Dapsone and Cyclophosphamide on Papilloma skin cancer in mice

Table 1

Effect of Dapsone and Cyclophosphamide on Papilloma skin cancer in mice

Group	% Body Weight Before/After	Cumulative no. of Papillomas	Tumour Incidence %	Tumour Yield	Tumour Burden	Average Latent Period
I (n=10)	100/100	0	-	0	0	0
II (n=10)	100/100	0	-	0	0	0
III (n=10)	100/100	0	-	0	0	0
IV (n=10)	100/87.5	25	100	3.8±0.46	3.8±0.46	7.43±0.41
V (n=10)	100/91.25	14	40	1.89±0.75	2.9±0.57	8.36 ±0.38
VI (n=10)	100/91	17	50	1.82±0.71	2.7±0.54	8.31±0.32

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