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Studies with MPG Against the Side Effects of Cyclophosphamide (Endoxan)-- A Preliminary Study

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SUMMARY

The alteration in the total leucocyte count was studied in Swiss albino mice and Albino rats after a single i.p. injection of Endoxan with or without MPG. It was found that MPG post-treatment reduced the incidence of leucopenia induced by Endoxan in mice and rats. The interaction of MPG and Endoxan (with different doses) was also investigated in terms of mortality during seven days. It was noted that MPG treatment enhanced the survival of mice against Endoxan induced mortality. These preliminary data suggest that MPG may interact with Endoxan damage in the same way as it interacts with radiation damage.

Various chemotherapeutic agents are now available for the treatment of cancer. However, the therapeutic dose and toxic dose of most of them overlap very much, so that margin of safety is so thin with regards to most of the anticancer drugs. A number of investigators are working on with a view to find out a suitable drug against the cytotoxic effects of anti-cancer drugs to healthy tissues. We had selected a synthetic SH compound MPG (2 mercaptopropionyl glycine) to test against the side effects of anticancer drug Endoxan. MPG is a potent antitoxic, clinically used in various hepatic disorders and effective at a very low non-toxic dose of 20 mg/kg b. wt., far below its toxic dose i.e. 2100 mg/kg. b. wt., 1, 2, 13, 14, 16. MPG is capable of liberating of SH group which has an important physiological function in the human body as an antitoxic agent and is an enzymatic activator. Our previous studies have shown that MPG modifies radiation damage in vivo *by reducing the death of animals and provide effective protection to the various tissues of mice against gamma rays injury. The present study was undertaken with a view to find out the modifying properties of MPG for anti-cancer drugs. In this paper we are publishing preliminary results obtained with MPG against the side effects of Endoxan in mice.*

MATERIAL & METHODS

Adult Swiss Albino mice weighing 22±4 gm were selected from an inbred colony, maintained on standard mice feed and water *ad libitum*. Animals were injected with 200, 300, 400 and 500 mg/kg b.wt. of Endoxan ASTA (Khandelwal Laboratories Pvt. Ltd., Bombay) intraperitoneally. Twenty to fourty minutes after the injection of Endoxan, animals were divided into two groups of equal numbers. One group was injected, with 20 mg/kg b.wt. of MPG (Santen Pharmaceutical Co. Osaka, Japan), dissolved in double distilled water and Ph adjusted to 6.5 with dilute solution of NaOH) intraperitoneally. The post-treatment symptoms and mortality were observed upto 7 days (Tab-1). A separate experiment conducted to find out the incidence of leucopenia in mice and Albino rats after Endoxan treatment in presence or absence of MPG. For this purpose, mice and rats were subjected to 100 and 200 mg/kg b.wt. of Endoxan in presence or absence of 20 mg/kg b.wt. of MPG respectively. (Tab-1). The peripheral blood drawn from the caudal vein and the total leucocyte count were performed on day 3 with the help of a hemocytometer.

RESULTS

The symptoms of Endoxan induced sickness i.e. shivering, ruffling of hair and epilation were observed in Endoxan treated animals. The general condition and weight of the animals were also lower, in case of Endoxan treated ones. In the animals treated with MPG, the onset of Endoxan induced sickness was delayed. The symptoms were of the same type in the MPG as well in the Endoxan alone treated control groups, but they were less severe in magnitude. The symptoms were much reduced in the animals receiving lower doses of Endoxan in presence of MPG.

The mortality data indicate that MPG enhanced the survival of mice against the Endoxan induced mortality.

TABLE I

ENDOXAN INDUCED MORTALITY IN MICE AND ITS MODIFICATION BY MPG (10 animals perpoient)

	Number of animals dying/day							
	1	2	3	4	5	6	7	No. of Survivors on day 7
ENDOXAN 500	6	—	1	1	0	1	—	1
ENDOXAN 500 + MPG	4	—	1	1	1	—	1	2
ENDOXAN 400	2	—	—	—	1	—	1	6
ENDOXAN 400 + MPG	1	—	—	—	1	—	1	7
ENDOXAN 300	—	1	—	—	2	—	—	7
ENDOXAN 300 + MPG	—	—	—	—	1	—	—	9
ENDOXAN 200	—	—	—	—	—	1	—	9
ENDOXAN 200 + MPG	—	—	—	—	—	—	—	10

(Table-1). The protection against mortality was observed in all the different doses of Endoxan treated animals in presence of MPG. It was also noted that mortality was higher on day one after the treatment in both groups. Second phase of mortality was recorded between days 5 to 7 after treatment (Table-1).

The leucocyte count in mice as well as in rats was higher in MPG treated groups in comparison to only Endoxan treated animals. A significant difference between the two groups was observed in both mice and rats.

DISCUSSIONS

The symptoms of Endoxan induced sickness in the present study, are in general agreement with the previous findings of Jagetia *et al* and Saharan *et al* with radiation induced sickness in mice Jagetia, acute 1981. They observed body weight loss, diarrhoea, increasing lethargy, ruffling of hair and epilation induced by radiation. In the present study the post-treatment with MPG, delayed the onset of Endoxan induced sickness and mortality is an accordance with the radiation induced sickness under the influence of MPG. The increased survival in MPG protected group in the present study may be due to the protection of GI tract and Hematopoietic organs by MPG. Protection of intestinal epithelium by MPG after different doses of irradiation has been reported by various workers.

In the present study, a significant elevation in leucocyte count may be due to protection of hematopoietic organs by MPG against the toxic effects of Endoxan. The leucocyte protection can be comparable with our earlier findings on the effect of radiation on hematopoietic organs and peripheral blood. Kumar and Uma Devi reported that the drug (MPG) significantly brought down the number of degenerating cells in the peripheral blood even at the early post-irradiation intervals. Further Kumar *et al* observed MPG reduced the early cell killing effects of gamma rays in thymus and also hastened recovery by accelerating mitotic activity both in medulla and cortex and reducing cell death, especially in cortex at later intervals. Kumar (1983) sug-

TABLE 2

TOTAL LEUCOCYTE COUNT (PERCENTAGE) CHANGES IN MICE AND RATS AGAINST CYCLOPHOSPHAMIDE (ENDOXAN) AND ITS MODIFICATION BY MPG ON DAY 3

Values before treatment	Groups	Mice	Rats
100%	Control	71.69 ±4.52	28.04 4.14
100%	Experimental	92.13 ±4.86	41.73 3.18
		$P < 0.02$	$P < 0.05$

Control — only Endoxan
Experimental — Endoxan + MPG

gested that the depopulation of total leucocyte in the peripheral blood of irradiated mice may be partly be attributed to the radiation effect on the blood forming organs and also to a direct destruction of blood cells. This hypothesis may be comparable in the case of Endoxan induced depopulation in leucocyte count in the present study.

In conclusion, MPG appears to modify Endoxan damage *in vivo* in much the same way as it modifies radiation damage. Further studies with the aim to established present results and to find out the best mode of MPG treatment are in progress.

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