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ABSTRACT

The presence of hypoxic and radioresistant cells is considered the main reason of failure in radiotherapy of neoplasms. Hypoxic cell radiosensitizers, as nitroimidazole derivatives, have an advantage over other alternative methods for improving the effects of radiotherapy since hypoxic cells exist in considerable concentration in tumours and only in small concentration in normal tissues. Its show also a direct cytotoxicity over the hypoxic cell population. In this work, studies on combining ip administered drugs and single dose radiation treatments in healthy albino mice are presented. It was compared the action of 2-nitroimidazole, levamisole and cysteine, the latest considered as radioprotector for several biological systems. The results showed some radioprotective action for 2- nitroimidazole (MISO), sensitizer capacity for levamisole and in those conditions, cysteine failed to produce any effects on the survival of 9 Gy ^{60}Co irradiated mice.

EFEITOS DE DERIVADOS DO IMIDAZOLE NA SOBREVIDA DE CAMUNDONGOS IRRADIADOS COM ^{60}Co

RESUMO

A presença de células radioresistentes e hipóxicas é considerada o principal motivo de fracasso na radioterapia de neoplasmas. Radiosensibilizadores de células hipóxicas, como os derivados do nitroimidazol, tem uma vantagem sobre outros métodos alternativos para melhorar o efeito da radioterapia pois as células hipóxicas existem em concentrações consideráveis em tumores e em pequenas concentrações nos tecidos normais. Esses compostos mostram também uma citotoxicidade direta sobre a população de células hipóxicas. Neste trabalho, são apresentados os estudos com tratamento combinado de drogas administradas ip e com dose unica de radiação gama em camundongos albinos sadios. Foram comparadas as ações de 2-nitroimidazol, levamizole e

cisteina, este último considerado radioprotetor em vários sistemas biológicos. Os resultados mostram alguma ação radioprotetora para 2- nitroimidazol (MISO), capacidade sensibilizadora para levamizole e naquelas condições, a cisteina não alterou a sobrevida de camundongos irradiados com 9 Gy ^{60}Co.

INTRODUCTION

Numerous radiation responses can be modified by chemical agents which means modifying recovery from or the full expression of damage after radiation exposure. Misonidazole, the 2-nitroimidazole (MISO), is one of a group of compounds which sensitise the normally radioresistant hypoxic tumour cells to radiation and are therefore potentially very useful in radiotherapy (McNally and col., 1978; Adams, 1979; Hofer and col., 1978).

The aim of this work was to assess the effect of low doses of two imidazole derivatives, which had been used for years as antiparasitic or antimicrobial agents, on the survival of whole-body gamma-irradiated mice. As comparison, experiments which a known radioprotector had been carried out.

MATERIAL AND METHODS

Conventional male or female albino mice from our animal house were used. They were housed in plastic cages maintained on usual mouse pellets and water ad libitum. The animals were 7 to 10-week-old at the start of the experiment.

The in vivo radiosensitization studies were performed testing three different compounds. With the exception of time delay after injections, the treatment design was identical in all experimental groups. Misonidazole (2-nitroimidazole Sigma), was dissolved in warm physiologic saline and injected i p . Groups of 20 mice injected with single doses of MISO received 0.5 mg/0.5 ml two hours before irradiation, whereas levamisole (L(-) 2, 3 , 5, 6-tetrahydro-6-phenylimidazo (2,1-6) thiazole) Janssen Phamaceutical , Johnson, & Johnson, 0.1 mg/0.1 ml was administered i p 30 min. prior irradiation. Single doses of 15 mg/0.5 ml of cysteinium chloride Merck were given i p to another group of animals 30 min. before irradiation. Each experiment was conducted with its own corresponding control.

^{60}Co radiation was delivered by a Gammacell 220 Irradiation Unit from Atomic Energy of Canada Ltd. During whole-body irradiation, the mice moved unrestrained in a cardboard (9 x 18) cm cylinder in groups of no

more than 3 aminals. The average rate dose was 375 Gy/h.

RESULTS AND DISCUSSION

Radiation lethality in mammals occuring at 10 - 20 days post irradiation is associated with failure of the haemopoietic stem cell populations to survive and proliferate (Bacq & Alexander, 1961). Influence of single i p injections of MISO, levamisole and cysteine on radiosensitivity of mice was investigaded. Fig 1A shows time-survival curves for mice irradiated in the gamma source with 8.5 Gy. The solid line indicates the survival of control irradiated mice during this experiment, while the dashed line indicates the survival of mice that had been irradiated with previous administration of MISO. The differences observed between both curves followed the pattern obtained for a radioprotective behaviour, with a 25% increase in the number of survivors.

In contrast, prior administration of levamisole produced a radiosensitization of about 20% in irradiated mice (Fig 2A). By comparison, Fig 3A shows the survival data for cysteine injected mice. In this case, no radiomodifier capacity can be attributed to cysteine, although in other systems this aminoacid showed radioprotective bahaviour.

Figures 1B, 2B and 3B show the variations of body-weight of mice involved in the corresponding experiments. At the end of the 30-day experiments, frequently the corporal weight seemed to recover the tendency to improve as much as the control.

Levamisole had been described by others (Dobbs et al, 1981) as having radioprotective properties. However, ours results shown a slight radiosensitizer behaviour when tested in female mice. That might be explain by differences in the biological system used, differences in male and female radiation response (Mickley, 1980) or even to the utilization of different strains of experimentation animals.

The behavior of MISO as a moderate radioprotector was also described on radiation-induced micronuclei formation in normal mouse bone marrow (Uma Devi et al, 1987). In that case, the drug did not increase the frequency of micronuclei, but produced a slignt reduction in their number, indicating a mild protective effect on normal chromosomes.

Although MISO has been shown to be a highly effective radiosensitizer of a wide spectrum of animal tumors and also active against human malignancies, its neurological toxicity is a severe limitation to the required drug levels and hence the degree of radiosensitization that can be achieved

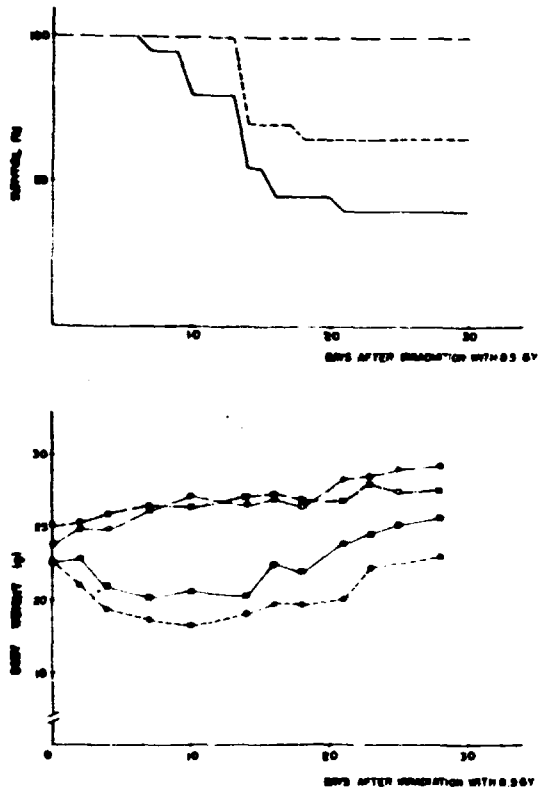

Fig 1.A) Radiation of 7 - week old male mice.

B) Thirty-day changes in body weight: (o—o—o) control; (■——■) irradiated; (□—□) MISO control and (●—●) MISO preteated + irradiated.

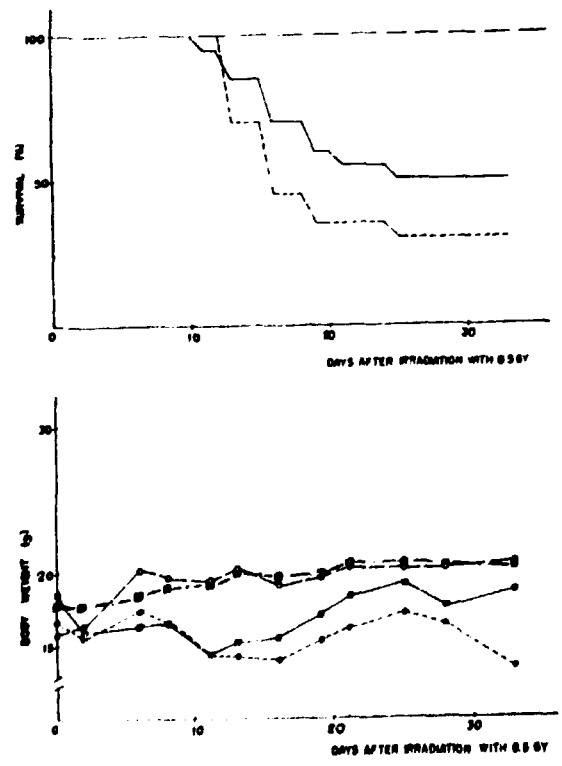

Fig 2.B) Radiation survival of 7-week old female mice.

B) Thirty-day changes in body weight: (o—o—o) control; (■——■) irradiated; (□——□) levamisole control and (●—●—●) levamisole pretreated + irradiated.

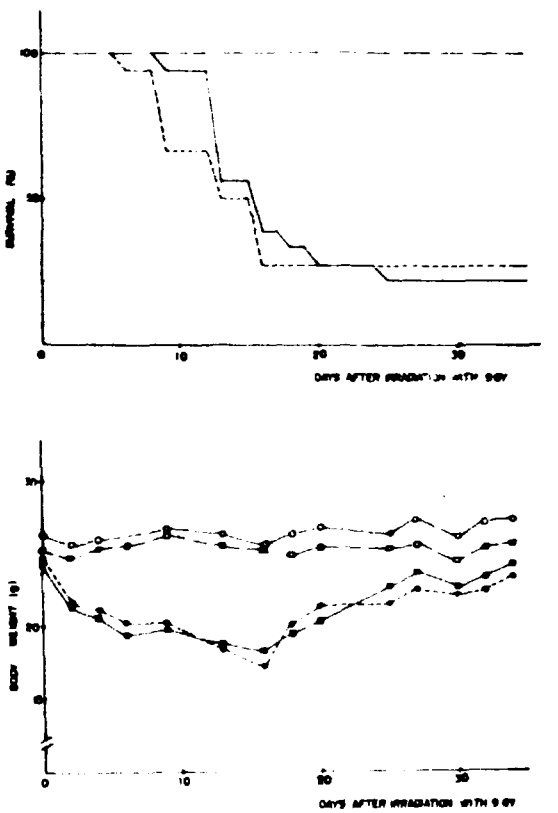

Fig 3.A) Radiation survival of 10-week old male mice.
B) Thirty-day changes in body weight: (o—o) control;
(□—□—□) cysteine control: (■— ■—■) irradiated and
(●—●—●) cysteine pretreated + irradiated.

(Travis, 1982). To limit the penetration of radiosensitizers in the neural tissue, the possiblility of using nitroimidazoles with a lower lipophili - city than MISO is been considered (Brown and col., 1981). Some authors also suggested the use of 2-nitroimidazole nucleoside that seems to be highly effective as a hypoxic cytotoxic agent (Agrawal and col., 1986).

Anyway, most of the studies of radiomodifiers have been performed in vitro, leaving their relevance to whole organisms to be ascertained. This work shows that a systematic study of the role of imidazole derivatives in modifying radiation response is needed before any conclusion can be drawn.

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