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REDUCTION OF RADIATION LETHALITY IN DOGS BY CHEMICAL MIXTURE

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Study of Protective Agents

Task 04

Biological and Medical Aspects of Ionizing Radiation

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Report No. 484

USAMRL Project No. 6X64-14-001-04

ABSTRACT

REDUCTION OF RADIATION LETHALITY IN DOGS BY CHEMICAL MIXTURE

OBJECT

To determine whether the pre-irradiation administration of mixtures of chemical agents to dogs, with or without post-irradiation supportive therapy, can provide effective protection from supra-lethal total-body doses of ionizing radiation.

RESULTS AND CONCLUSIONS

A total of 68 small dogs were individually exposed to supra-lethal doses of 600 r ($1.8 \times LD_{100}$) of acute whole-body radiation from a cobalt 60 source. The administration of 4 to 5 mg/kg of para-aminopropiophenone (PAPP) intravenously 30 minutes before, and 225 mg (total dose) of S, β -aminoethylisothiuronium (AET) plus 32.5 mg (total dose) of serotonin intraperitoneally 10 to 15 minutes before irradiation provided 58 per cent survival, whereas the administration of PAPP alone protected only 13 per cent. By supplementing this pre-irradiation chemical treatment with post-irradiation supportive therapy consisting of antibiotics, vitamins, parenteral fluids, and whole-blood transfusions, the survival of the PAPP treated dogs was increased to 63 per cent, while the survival of the dogs receiving the chemical mixture was increased to 82 per cent. Post-irradiation supportive therapy increased the mean survival time of control irradiated dogs by 4 days, but effected survival beyond 30 days in only one case. Pre-treatment with chemical agents seemed to influence favorably the post-irradiation fall in leucocytes, but did not noticeably effect the hematocrit or hemoglobin levels. No deaths occurred as a direct result of the toxicity of the chemical agents; furthermore, the intravenous administration of methylene blue immediately following irradiation rapidly reversed the toxic effects.

RECOMMENDATIONS

It is recommended that this and other mixtures of chemical radio-protective agents be investigated further in dogs with a view toward possible human application.

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REDUCTION OF RADIATION LETHALITY IN DOGS BY CHEMICAL MIXTURE

I. INTRODUCTION

Effective protection from radiation induced lethality in rodents by the pre-irradiation administration of various chemical agents has been demonstrated by numerous investigators. In this laboratory an improved degree of protection in mice against supra-lethal doses of whole-body X-irradiation has been achieved by the pre-irradiation administration of a mixture of radio-protective chemicals containing S. β -aminoethylisothiuronium (AET), β -mercaptoethylamine (MEA) and serotonin (1). By supplementing the above chemical treatment with the use of lead-grid partial-body shielding during irradiation or the transplantation of isologous bone marrow following irradiation, further increases in the survival of mice at supra-lethal doses of X-radiation were obtained (2, 3).

Attempts to protect dogs from radiation induced lethality using single chemical agents have been rather disappointing (4); however, using a mixture of AET and para-aminopropiophenone (PAPP), Blouin and Overman, in a preliminary paper, reported 83 to 100 per cent survival in dogs following exposure to 500 r ($1.25 \times LD_{100}$) of X-radiation (5). Similarly, Jacobus used high doses of MEA and cysteine combined to protect dogs against 700 or 775 r of X-rays (6).

It has been reported that streptomycin and bone marrow therapy in mice following supra-lethal X-irradiation enhances the protection afforded by pre-treatment with AET (7). Furthermore, the beneficial effects of post-irradiation therapy with antibiotics, vitamins, and whole blood transfusions have been demonstrated in sublethally irradiated dogs (8-12). The effectiveness of such post-irradiation therapy in chemically protected, supra-lethally irradiated dogs has not previously been reported in the literature.

The present study was undertaken to determine, firstly, the degree of radiation protection which could be obtained in dogs by the prior administration of a mixture of chemical agents; and, secondly, the effect of post-irradiation supportive therapy on the percentage of survival of chemically pre-treated, irradiated dogs.

II. EXPERIMENTAL

A total of 68 healthy, mature, mongrel dogs of both sexes, weighing 6.5 to 11.0 kg were used in this study. All dogs were individually

exposed to supra-lethal doses of 600 r of acute whole-body radiation from a cobalt 60 source. The dogs to be irradiated were assigned randomly to the following groups:

- Group I. Control (No Pre-treatment)
 - a. With post-irradiation supportive therapy
 - b. Without post-irradiation supportive therapy
- Group II. Pre-treatment with PAPP
 - a. With post-irradiation supportive therapy
 - b. Without post-irradiation supportive therapy
- Group III. Pre-treatment with PAPP, AET and Serotonin
 - a. With post-irradiation supportive therapy
 - b. Without post-irradiation supportive therapy

Prior to their use in this study, the dogs were quarantined for two weeks, given anthelmintics and vaccinated against canine distemper, hepatitis, and rabies. They were then moved to individual metal cages in an air-conditioned building and observed for an additional week. One pound of a commercial canned dog food was fed daily and free access to drinking water was allowed. The cages were cleaned and chemically disinfected each day. Preceding irradiation, the food consumption, nature of the feces, rectal temperature, and heart rate were recorded daily, and control blood determinations of hematocrit, hemoglobin, total and differential leucocyte counts were obtained. Dogs exhibiting abnormal clinical or blood pictures were excluded from the study. All food was withheld for 24 hours before irradiation.

A 1000 curie cobalt 60 irradiation facility was used as the source of ionizing radiation (13). Each dog was placed in a single compartment lucite cage, rotated on a platform at three revolutions per minute, and exposed to 600 r of total-body radiation (mid-tissue dose) from above. The source to mid-tissue distance was 54.5 cm. Prior to each series of irradiations the mid-tissue dose rate (27 to 32 r/min) was determined in a rectangular paraffin dog phantom with a 100 r Victoreen thimble chamber. The details of dosimetry and specifications of the radiation cage were described in a previous paper (14).

The doses of the chemical agents used in this study and the interval between the administration of the chemical mixture and the time of irradiation were derived from the results of preliminary experiments in dogs in which the protective capabilities of various individual and combined chemical agents were tested.

The chemical agents tested were para-aminopropiophenone (PAPP)¹, S, β -aminoethylisothiuronium (AET)², and 5-hydroxytryptamine (serotonin)³. All solutions were prepared aseptically within five minutes of their intended use. The PAPP was dissolved, with slight warming, in propylene glycol at a concentration of 10 mg/ml. The AET and serotonin were dissolved together in 3 to 5 ml of normal saline and the final mixture adjusted to a pH of 6.3 to 6.6. A one per cent solution of methylene blue was prepared in normal saline. The PAPP was administered by slow intravenous injection 25 to 30 minutes before irradiation at doses of 4 to 5 mg/kg of body weight. The mixture containing a total dose of 225 mg of AET and 32.5 mg of serotonin per dog was administered intraperitoneally 10 to 15 minutes before irradiation. Immediately following irradiation methylene blue at a dose of 2 mg/kg was administered intravenously to those dogs which had previously received PAPP.

The groups of dogs designated to receive post-irradiation supportive therapy were treated according to the following regimen:

a. Antibiotics: Antibiotics were administered only after an elevation of the rectal temperature above 102.5°F was noted. Initially 300,000 units of procaine penicillin G plus 0.5 gm of streptomycin sulfate were administered intramuscularly once daily. If no response was observed in 24 hours, the dosage was doubled. On the subsequent day, if no reduction in rectal temperature was noted, chlortetracycline or oxytetracycline (250 to 500 mg per day) were added to the treatment, given orally if tolerated, or otherwise intravenously. The antibiotic therapy was continued until death, or until an improved clinical condition and a rising leucocyte count indicated recovery.

b. Parenteral Fluids: 150 to 300 ml of 15 per cent dextrose in saline intravenously by slow drip, or 150 to 300 ml of 5 per cent dextrose in water subcutaneously were administered to the dogs once daily only when they refused all food. These parenteral fluids were supplemented with potassium chloride (10 meq/l), vitamins C and B complex, and broad spectrum antibiotics. As blood electrolyte determinations were not made in this study, identical solutions were administered to all dogs without attempting to correct the fluid and electrolyte balance of each dog individually.

¹Obtained from Eastman Kodak Company, Rochester, N. Y.

²In the form of the Br·HBr salt, obtained from Schwarz Laboratories, Mount Vernon, N. Y.

³In the form of the creatinine sulfate salt, obtained from the California Foundation for Biochemical Research, Los Angeles, Calif.

c. Miscellaneous Treatments: Other therapy was given as indicated by the development of clinical symptoms. A gastrointestinal adsorbent (Kaopectate, Upjohn) was given orally when diarrhea was noted, and topical antibiotics and cutaneous wound therapy were used when skin infections were present. All dogs in the treated group were given 0.5 ml/kg of body weight of hyperimmune serum (anti-canine distemper, hepatitis, and leptospirosis) subcutaneously at 14-day intervals following irradiation.

Following irradiation the food consumption, rectal temperature, and nature of the feces of both treated and untreated dogs were recorded daily. Every 3 to 5 days blood was collected for the determination of hematocrit, hemoglobin, and total and differential leucocyte count. Deaths were recorded daily. The dogs living beyond 30 days were counted as survivors and were retained for future study. All dogs which died following irradiation were necropsied.

III. RESULTS

In this study 68 dogs were exposed to 600 r of acute whole-body radiation from a cobalt 60 source. Under identical conditions of irradiation the LD_{50/30 days} was previously estimated at 260 r, and the LD_{100/30 days} at 325 r (14).

The data from individual dogs used in this study are presented in Table 1, summarized in Table 2, and graphically illustrated in Figure 1. Cumulative mortality is illustrated in Figures 2 and 3. The results of irradiating the different groups of dogs are as follows:

Group I: Among the 18 irradiated controls of 6 dogs receiving no post-irradiation supportive therapy all died, and only one of the 12 dogs receiving post-irradiation therapy survived; however, this survivor exhibited very severe signs of radiation injury, including its total refusal of food intake for 17 days, before its ultimate recovery. At the 12th post-irradiation day the cumulative mortalities were found to be 100 per cent for those without, and only 25 per cent for those with supportive therapy. The mean survival time of the non-survivors in this group was 10.7 days for those without and only 14.5 days for those with post-irradiation supportive therapy.

Group II. A total of 16 dogs were given PAPP intravenously prior to radiation exposure. Five of the 8 dogs receiving post-irradiation supportive therapy survived (62.5 per cent), while only 1 of 8 survived without supportive therapy (12.5 per cent). The mean survival time of

TABLE 1

INDIVIDUAL MORTALITY DATA FOR DOGS IRRADIATED AT 600 r COBALT 60

Group IA. Control without pre-radiation chemical but with post-radiation therapy.

Dog No.	Sex	Body Wt. (kg)	Days Survived	Dog No.	Sex	Body Wt. (kg)	Days Survived
10	F	8.1	25	514	M	11.0	9
13	F	8.3	19	659	M	10.0	15
172	F	7.2	4	700	M	9.6	17
389	M	8.7	12	776	M	10.9	16
391	F	8.3	15	806	F	9.8	30+
465	M	10.1	13	838	F	10.0	14

Group IB. Control without pre-radiation chemical and without post-radiation therapy.

Dog No.	Sex	Body Wt. (kg)	Days Survived	Dog No.	Sex	Body Wt. (kg)	Days Survived
103	F	6.5	11	943	M	10.6	12
121	F	8.1	9	944	M	8.4	12
942	M	8.6	9	B-106	F	9.8	11

Group IIA. PAAP 5 mg/kg I.V. with post-radiation therapy.

Dog No.	Sex	Body Wt. (kg)	Days Survived	Dog No.	Sex	Body Wt. (kg)	Days Survived
452	F	9.8	15	774	M	11.0	30+
632	F	10.2	15	910	F	9.3	15
657	M	9.6	30+	916	F	10.2	30+
717	F	7.5	30+	941	M	9.6	30+

Group IIB. PAAP 4 mg/kg (*) or 5 mg/kg I.V. and 225 mg AET plus 32.5 mg serotonin I.P. with post-radiation therapy.

Dog No.	Sex	Body Wt. (kg)	Days Survived	Dog No.	Sex	Body Wt. (kg)	Days Survived
549	F	8.9	11	687*	F	10.9	30+
545	M	11.0	30+	701	M	8.6	30+
596	M	10.6	30+	710	F	10.0	18
615	F	9.6	30+	729	M	8.0	11
635	F	9.7	30+	730	M	9.0	17
650	F	10.2	30+	775*	M	10.9	30+
651	M	9.4	30+	778	M	10.0	30+
652	F	10.9	30+	795*	M	8.4	30+
654	F	11.0	30+	797*	M	8.4	30+
661	M	9.1	30+	810*	F	7.7	30+
685*	M	9.8	30+	833*	M	8.0	30+

Group IIB. PAAP 4 mg/kg (*) or 5 mg/kg I.V. and 225 mg AET plus 32.5 mg serotonin I.P. without post-radiation therapy.

Dog No.	Sex	Body Wt. (kg)	Days Survived	Dog No.	Sex	Body Wt. (kg)	Days Survived
314*	F	8.2	18	655	F	8.5	30+
559	M	10.5	15	656	M	10.5	30+
609	F	10.3	30+	658	M	10.7	30+
617	F	10.0	30+	852*	M	8.8	20
619	F	8.4	12	890*	M	8.9	12
634	F	8.2	30+	895*	M	10.2	30+

TABLE 2

SUMMARY OF DRUG PROTECTION STUDIES IN DOGS (600 r COBALT 60)

Pre-radiation Treatment	Group	Post-radiation Therapy	No. of Dogs	No. of Survivors	Mean Survival Time (Days) (Non-surr. Only)	Per cent Survival
Control	I A	Yes	12	1	14.5	8.3
	I B	No	6	0	10.7	0
PAAP (I.V.)	II A	Yes	8	5	14.3	62.5
	II B	No	8	1	12.6	12.5
PAAP (I.V.) and AET + Serotonin (I.P.)	III A	Yes	22	18	14.3	81.8
	III B	No	12	7	15.4	58.3

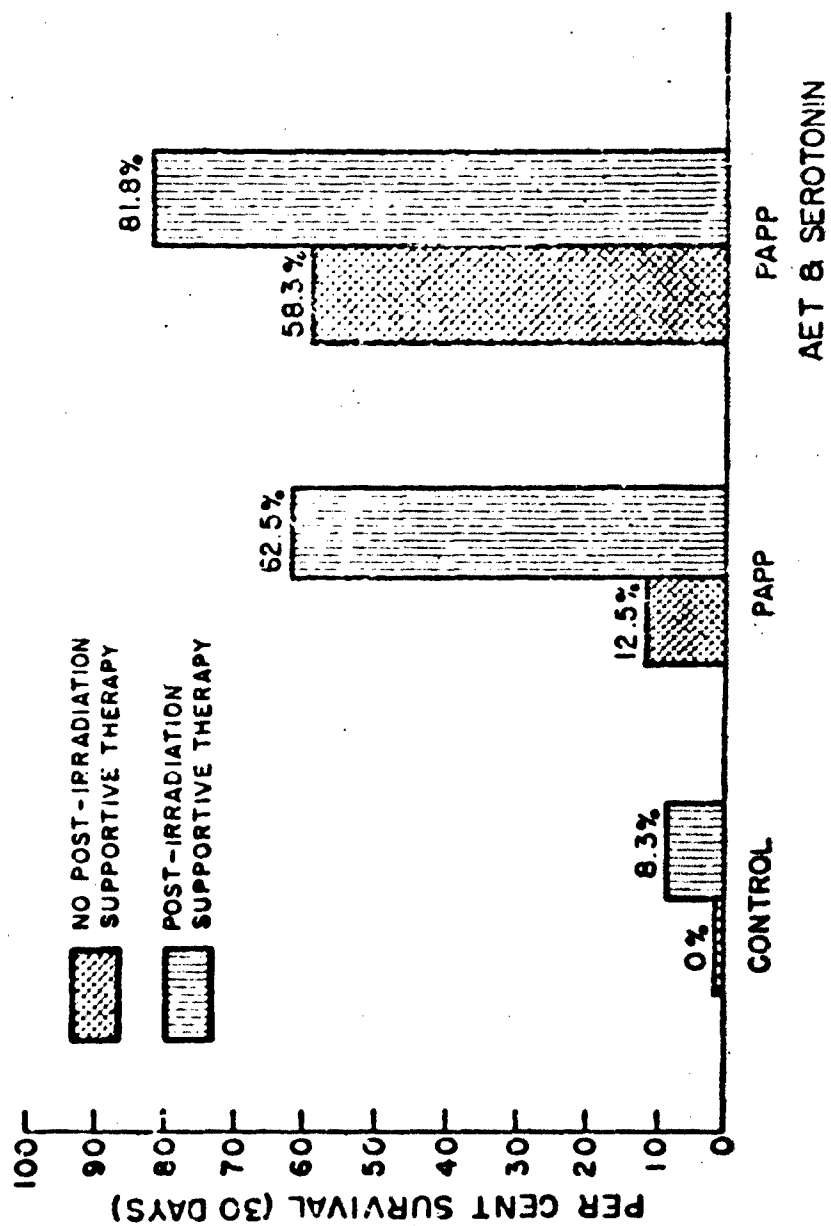


Fig. 1. Thirty day survival of control and chemically protected dogs following 600 r of acute whole-body radiation.

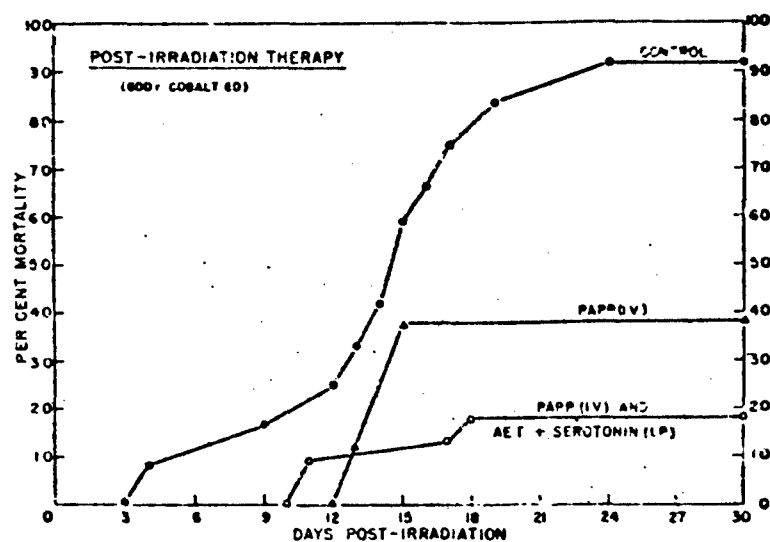


Fig. 2. Cumulative mortality of control and chemically protected dogs following 600 r and with post-irradiation supportive therapy.

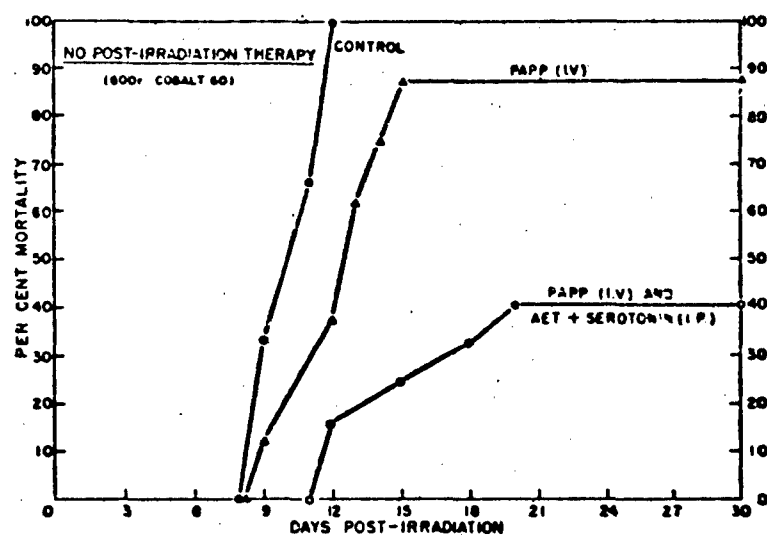


Fig. 3. Cumulative mortality of control and chemically protected dogs following 600 r but without post-irradiation supportive therapy.

the non-survivors in this group was not markedly influenced by the supportive therapy. The 50 per cent added survival of those receiving supportive therapy was the result of a large reduction in the number of deaths occurring between the 12th and 15th post-irradiation days.

Group III. A total of 34 dogs were given PAPP intravenously and AET plus serotonin intraperitoneally before irradiation. Eighteen of the 22 dogs with post-irradiation supportive therapy survived (81.8 per cent) as compared to only 7 survivors among 12 dogs without post-irradiation supportive therapy (58.3 per cent). The 23.5 per cent added mortality among those receiving no supportive therapy occurred between the 12th and the 18th post-irradiation days. Again no marked difference in the mean survival time among the non-survivors in this group was noted.

The immediate side-effects following the administration of these chemical agents varied from mild to severe signs of toxic reaction characterized by cyanosis, dullness, weakness, hyperpnea, tachycardia, excessive salivation, straining, urination, and defecation. Occasionally these symptoms became severe enough to produce complete prostration. The intravenous administration of 2 mg/kg of methylene blue immediately following irradiation, however, rapidly abolished these toxic side-effects, and recovery was essentially complete within 3 to 4 hours. In spite of these toxic reactions, drug-induced mortality was not encountered in this study.

The average hematocrits and total leucocyte counts of the control and chemically treated dogs, regardless of eventual survival or non-survival, are illustrated in Figures 4 and 5. Following irradiation, a rapid fall in leucocytes, especially lymphocytes, was seen in all dogs. It appears that the irradiated controls (Group I) exhibited the greatest and most rapid drop in leucocytes, whereas the dogs receiving PAPP, AET, and serotonin (Group III) showed the least pronounced leucopenia. The leucocyte pictures of dogs receiving identical pre-irradiation treatment, with or without post-irradiation supportive therapy, were not noticeably different. The changes in the hemoglobin levels were found to be closely parallel to those of the hematocrit values and are not therefore included in the graphs. The hematocrit and hemoglobin levels decreased progressively following irradiation, but there were no apparent differences between the control and chemically protected dogs.

A comparison of the average hematocrit and leucocyte values of the survivors and the non-survivors within each group of control and chemically treated dogs is presented in Figures 6 to 11. The average leucocyte counts of the non-survivors fell well below those of the

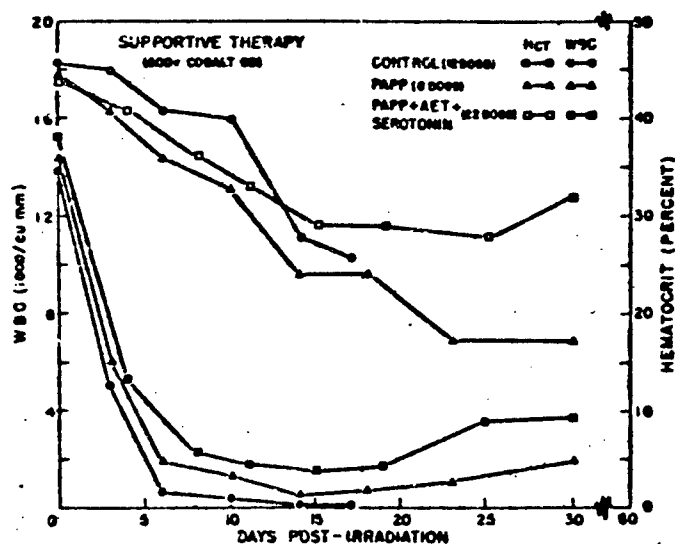


Fig. 4. Hematocrits and total leucocyte counts of control and chemically protected dogs receiving post-irradiation supportive therapy.

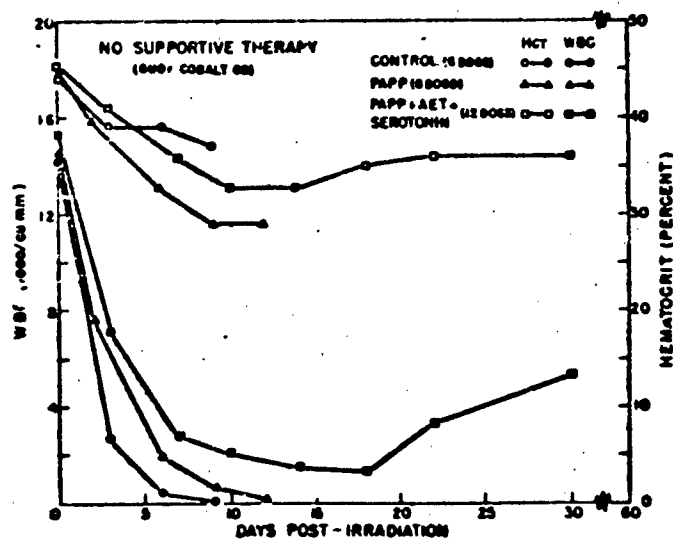


Fig. 5. Hematocrits and total leucocyte counts of control and chemically protected dogs receiving no post-irradiation supportive therapy.

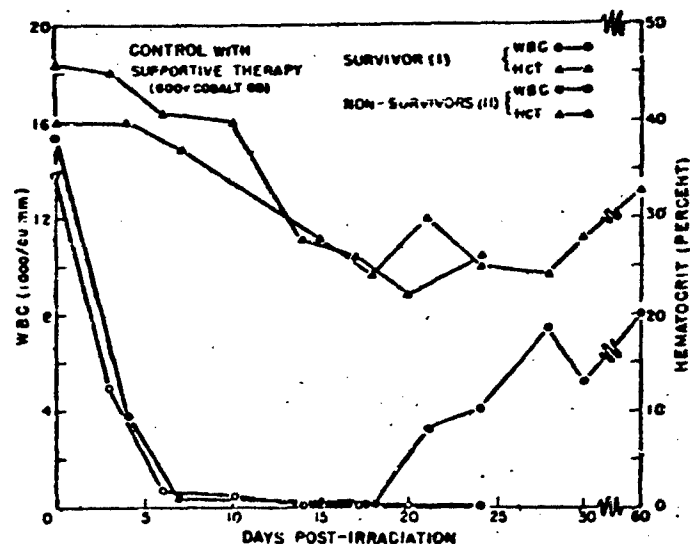


Fig. 6. Hematocrits and total leucocyte counts of the survivors and non-survivors in the group of control irradiated dogs receiving post-irradiation supportive therapy (Group Ia.).

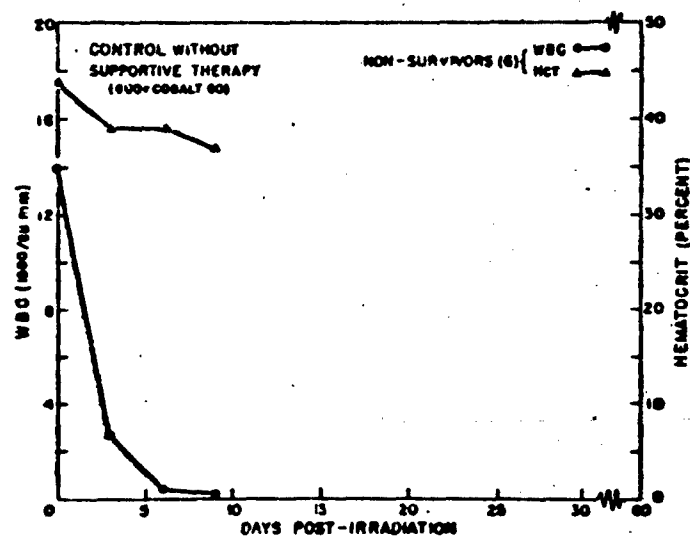


Fig. 7. Hematocrits and total leucocyte counts of the non-survivors in the group of control irradiated dogs receiving no post-irradiation supportive therapy (Group Ib.).

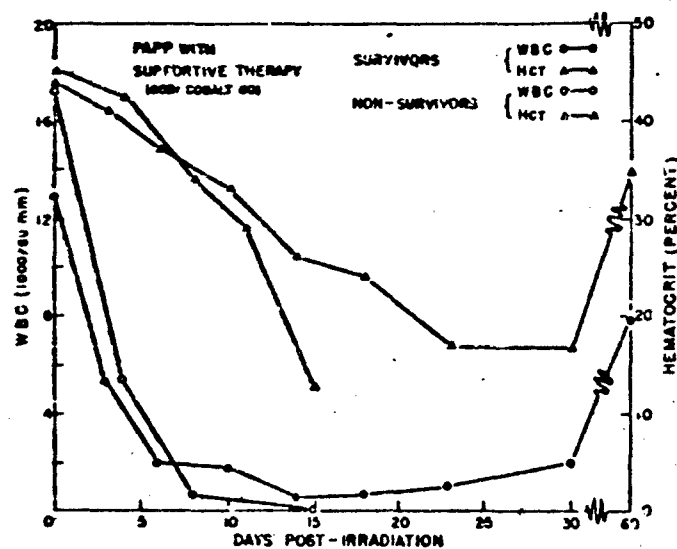


Fig. 8. Hematocrits and total leucocyte counts of the survivors and non-survivors in the group of PAPP treated dogs receiving post-irradiation supportive therapy (Group IIa.).

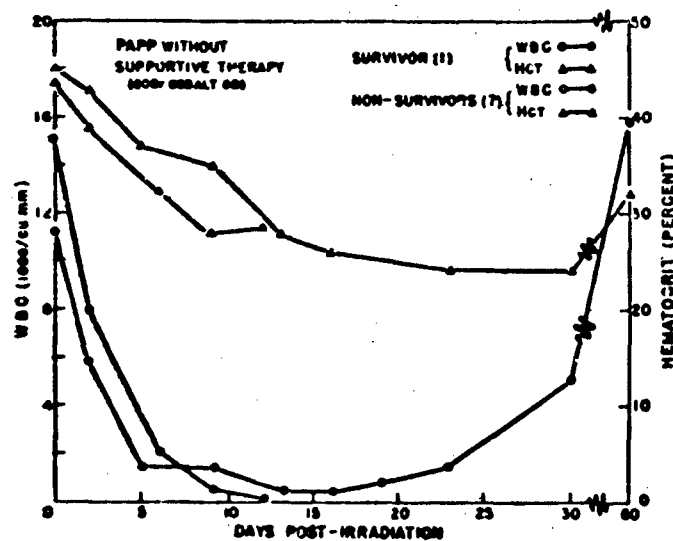


Fig. 9. Hematocrits and total leucocyte counts of the survivors and non-survivors in the group of PAPP treated dogs receiving no post-irradiation supportive therapy (Group IIa.).

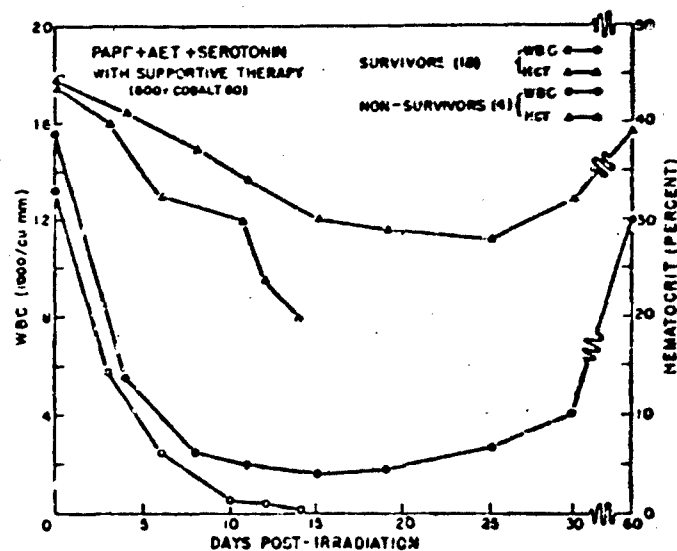


Fig. 10. Hematocrits and total leucocyte counts of the survivors and non-survivors in the group of dogs treated with PAPP, AET, and serotonin and receiving post-irradiation supportive therapy (Group IIIa.).

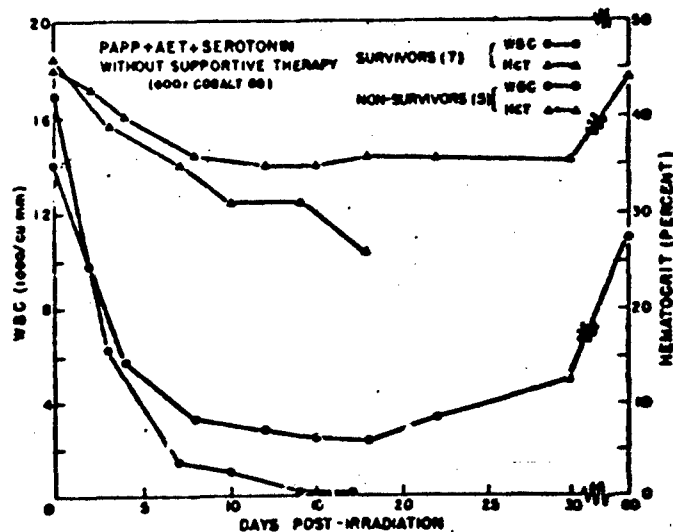


Fig. 11. Hematocrits and total leucocyte counts of the survivors and non-survivors in the group of dogs treated with PAPP, AET, and serotonin but receiving no post-irradiation supportive therapy (Group IIIb.).

survivors. The leucocyte counts of dogs which eventually survived began to rise after the second week, approaching pre-irradiation levels by 60 days. In general, the hematocrit and hemoglobin values decreased more rapidly among the non-survivors. The return of the hematocrit and the hemoglobin to pre-irradiation levels among the survivors was not always complete even after 60 days.

IV. DISCUSSION

Numerous chemical agents, including PAPP, AET, and serotonin, have been found to protect rodents from radiation induced lethality (16, 17, 21). However, such chemical agents were too toxic when administered to dogs in doses comparable on a weight basis to those used in rodents (4). On the other hand, the reduction of the dosages to less toxic levels resulted in greatly diminished or insignificant protective activity. At present, no single chemical agent has been shown to provide satisfactory radiation protection to dogs at non-toxic dose levels.

It has been demonstrated in mice that mixtures of chemical agents at a lower dosage for each offered, without additive toxicity, greater radiation protection than any one of the agents used alone (1). The successful use of mixtures of radio-protective agents in dogs has also been reported (5, 6).

The combination of chemical agents used in the present study was derived from earlier screening experiments in dogs at this laboratory. It was found that the pre-irradiation administration of PAPP (4 to 5 mg/kg) intravenously and AET (225 mg per dog) plus serotonin (32.5 mg per dog) intraperitoneally provided a high degree of protection from radiation induced lethality. The doses of these chemical agents given to dogs were about 10 to 50 times less than the doses required to produce effective radiation protection in mice (1). In spite of the development of toxic side-effects following the administration of this chemical mixture to dogs, no drug-induced mortality was encountered. Furthermore, much of the toxic effect resulted from PAPP-induced methemoglobinemia and could be reversed by methylene blue.

Little information is available concerning the exact mechanisms of the radio-protective action of PAPP, AET, and serotonin.

PAPP produces a rapidly developing, pronounced methemoglobinemia when administered intravenously to dogs (15). Its radio-protective activity has been explained on the basis of the resultant tissue hypoxia (16).

AET is among the most effective of the numerous amines and sulfhydryl compounds that have been tested for radio-protective activity in mice (17). It has been postulated that these compounds protect by virtue of their direct reaction with radiation-induced radicals, producing stable hybrids which then react preferentially with other radicals rather than with sensitive biological material. The isothiuronium group of AET is apparently responsible for its protective activity (18). In the present study, all solutions of AET were adjusted to a pH of 6.3 to 6.6 just before administration. AET transforms readily to 2-mercapto-ethylguanidine (MEG) at a pH around neutral (19). It is assumed therefore that some of the observed radio-protective effect was due to MEG.

It has recently been demonstrated that serotonin probably owes its protective activity to its ability to lower tissue oxygen tension in certain critical organs such as the spleen (20). This effect is apparently due to the smooth muscle effects of serotonin, producing vasoconstriction (21).

The beneficial effect of symptomatic post-irradiation supportive therapy in both control and chemically protected dogs is demonstrated in this study. By administering antibiotics, parenteral fluids, whole blood, and vitamins to supra-lethally irradiated control dogs, increase of 4 days in the mean survival time was noted, and in one dog, survival beyond 30 days was attained. The beneficial effect among the chemically protected dogs is evidenced by a large decrease in 30 day mortality.

A precise evaluation of each phase of the post-irradiation treatment program was not intended in the design of these experiments; however, the sequellae of hemorrhage, infection, and anemia occurring within the first 30 days after radiation were certainly altered by these treatments. On the basis of subjective clinical evaluation of the individual dogs in the treated and untreated groups, it is a general impression that, in untreated dogs in which the total leukocyte count fell below about 1000 per mm^3 , overwhelming infection leading to death was the invariable consequence. However, among the dogs receiving supportive therapy, the onset of overwhelming infection was often prevented or delayed by antibiotic therapy, even in the face of total leukocyte depression far below 1000 per mm^3 . Furthermore, even in cases where infection, hemorrhage and anemia developed to a degree producing a complete cessation of oral intake, it was occasionally possible to prolong life by the vigorous administration of electrolytes, glucose, vitamins, fluids, and whole blood until a subsequent rise in leukocyte count initiated the recovery process.

V. CONCLUSIONS

Effective protection of dogs from radiation induced lethality can be provided by the pre-irradiation administration of para-aminopropiophenone (PAPP), S β -aminoethylisothiuronium (AET), and serotonin in combination, whereas PAPP alone is relatively ineffective. This combination of chemical agents is only moderately toxic, and much of its toxic effect may be rapidly abolished by the administration of methylene blue following irradiation. Vigorous post-irradiation therapy with antibiotics, vitamins, parenteral fluids, and whole-blood markedly decreases the mortality among chemically protected dogs, and increases the survival time of unprotected dogs.

VI. RECOMMENDATION

It is recommended that this and other combinations of chemical agents be investigated further in dogs with a view toward possible human application.

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