ANTIHISTAMINE DRUGS AND RADIATION SICKNESS

BY

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Radiation sickness is a syndrome characterized in varying degree by drowsiness, fatigue, nausea, and vomiting. Indirect evidence in favour of the hypothesis that histamine plays a part in the production of this syndrome has been put forward by various workers (Segal, 1939; Leblond and Segal, 1942; Ellinger, 1945, 1946, 1948; Thygesen, 1947). The use of antihistamine drugs in the treatment of radiation sickness has been advocated by Lofstrom and Nurnberger (1946). These authors claimed that the administration of "benadryl" to patients who had developed radiation sickness resulted in a considerable amelioration of symptoms. However, in their paper not enough details were given of the factors governing x-ray dosage and there was no control series of cases. In view of this claim, and also of the possible significance of histamine in the production of radiation sickness, it was considered that a controlled clinical experiment was required to clarify the position.

Details of the Experiment

The antihistamine used was "anthisan," which has been shown to be the most potent and specific drug available (Schild, 1947; Gaddum, 1948). The patients used for the investigation were those undergoing post-operative irradiation with x rays for carcinoma of the breast. This form of treatment has been standardized in respect of duration of treatment, volume irradiated, and total dosage given (McWhirter, 1948). The 47 patients in this study were divided into three groups, as follows:

Group A.—Seventeen patients were given anthisan in doses of 0.6–1 g. daily. Ten of these received 1 g. daily and seven had 0.6 g. daily, these latter cases being unable to tolerate the higher dose. The active tablets were administered for five days before starting irradiation so that side-effects were minimized and an adequate concentration of anthisan was secured in the tissues.

Group B.—Fifteen patients were given an inactive preparation identical in appearance to the active preparation. This was also administered for five days before the beginning of irradiation.

Group C.—Fifteen patients were given no preparation at all.

In every case an assessment of the patient's clinical condition was made by one of us (W. M. C. B.) who was entirely ignorant of the type of tablet which the patient was being given. This assessment was made after every fifth treatment in respect of drowsiness, fatigue, headache, nausea, and vomiting. The results are shown in the Table:

Group	Total No. of Cases	No. Developing Radiation Sickness
A	17	16 (94.1%)
B	15	10 (66.6%)
C	15	11 (73.6%)

It will be noted that only a small number of patients have been studied in each group. The investigation had to be abandoned because many of the patients given the active drug became so upset after the starting of irradiation that they would have been unable to continue with x-ray treatment unless the drug had been withdrawn.

Toxic Effects.—Five out of the 17 cases receiving anthisan developed a toxic erythema accompanied by pronounced constitutional symptoms during irradiation. This patchy erythema, first noted in the posterior shoulder field between the third and fifth days after the beginning of x-ray therapy, spread centrifugally, becoming generalized over the greater part of the trunk and extremities after 48–72 hours. Withdrawal of the antihistamine drug at any stage in its development resulted in a rapid disappearance of the erythema even though x-ray therapy was continued. Such a skin rash never occurs with x-ray therapy alone, and is seen in less than 1% of cases receiving antihistamine drugs for other purposes.

Discussion

The important practical point that emerges from the study is that in spite of the small number of patients observed it can confidently be stated that anthisan is of no value in the treatment of radiation sickness. Any benefit which results from the administration of other antihistamine drugs is likely to be due to properties other than their antihistamine effect. In addition, not only did anthisan fail to prevent radiation sickness, but, as will be seen from the Table, it appears that those patients receiving the active drug showed a greater incidence of constitutional upset while having x-ray therapy than did either of the two control groups. The difference between Group A and the control series is not statistically significant, but was convincing enough to stop the trial of further cases.

There is considerable evidence to show that histamine may be released in animals in a variety of circumstances. The similarity which exists between the manifestations of certain human states and conditions that can be produced experimentally in animals has led to the belief that histamine plays an important part in certain disease processes. Dale (1948) has suggested that it may possibly have a physiological role in the control of capillary tone. Though there is no direct proof that histamine is released from the tissues by ionizing radiations, the presumption of such a release is an attractive hypothesis which explains many of the manifestations of radiation sickness.

This study seems to show that the administration of anthisan during irradiation with x rays produces a toxic erythema in some cases and may also give rise to a profound constitutional upset. Antihistamine drugs such as anthisan exert their effects by modifying the tissues in such a way that locally released histamine does not produce its pharmacological effects. It is suggested that the local release of histamine resulting from irradiation with x rays and leading to vasodilatation and alteration in capillary permeability may be of physiological importance, and that this type of reaction to injury may well play an important part in preserving the integrity of the organism. The administration of agents such as antihistamine drugs during irradiation may interfere with this protective mechanism, thus accounting for the marked effects noted in this study.

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