CHEMOPROPHYLAXIS AND CHEMOTHERAPY

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The activity of isatin-B-thiosemicarbazone against vaccinia virus was first described by Thompson and co-workers in the United States in 1953, using infected mice as their model. Subsequent work by Sadler & Bauer has revealed a number of derivatives possessing great activity and of these N-methyl-isatin-B-thiosemicarbazone was selected for chemoprophylactic study in a smallpox endemic area. Close contacts of established smallpox cases were divided into two random groups. Both groups were vaccinated, but only one group received the prophylactic drug. The other group either received nothing or was given a placebo. The members of each group were visited during the subsequent 16 day period when the last visit was made. Among 1101 contacts given N-methyl-isatin-B-thiosemicarbazone, three mild cases occurred, while in the control group of 1126 contacts, 78 cases arose, 12 of which ended fatally. The vaccination histories and distributions of both groups were identical. Bauer et al. showed that the chemoprophylactic effect was independent of any immunity acquired as a result of vaccination, since the incidence was markedly reduced in those contacts who had never been vaccinated (23 treated contacts resulting in no cases compared to 16 control contacts resulting in nine cases with four deaths), or contacts given primary vaccination after exposure irrespective of the result (79 treated contacts resulting in two cases, 84 control contacts resulting in 19 cases with seven deaths). In as much as treatment was begun on the day after the removal of the index case to the hospital, it can be assumed that the drug was given about the middle of the incubation period. Thus, the drug exerted its prophylactic action when given well into the incubation period and regardless of the patient's immunization status.
Untoward side-effects observed consisted principally of nausea and vomiting. These symptoms were occasionally severe, resulting in removal to a general hospital of four or five patients; however, the total number of untoward reactions is not certain. Some vomiting occurred in the placebo group as well, and generally on a family-wide basis. While, therefore, there is some suggestion that an emotional factor might be concerned in some of the untoward reaction, it is our impression that a very definite incidence of nausea and vomiting was experienced, particularly in the patients of the middle or upper economic class.

Currently, the studies are being repeated, utilizing a single day treatment as opposed to the three day treatment employed in the study described by Bauer et al.

A fairly extensive chemotherapeutic trial of a related compound is under way under the direction of Dr Ramachandra Rao. The results of this are not yet available.

The use of 5-Iodo-2'-deoxyuridine (IDU) which has been previously shown to cure or ameliorate herpes simplex infection of the cornea, has been extended to the vaccinia group of agents. Studies on vaccinia infections of rabbit cornea treated with IDU indicate that vaccinia keratitis is improved or clinically cured. In about one-half of the treated eyes no virus could be detected after treatment whereas virus was present in all control eyes.

Additionally, a good deal of work has been done by Calabresi, McCollum & Walsh of Yale in an attempt to extend previous studies on IDU from the cancer field into that of viral chemotherapy. Their experiments deal with the systemic administration of iodinated pyrimidine deoxyribonucleosides. They describe favourable results obtained with parenterally administered IUdR in the treatment of artificially induced intradermal vaccinia infection in rabbits and in man. The material has been administered systemically only to patients with metastatic neoplastic disease. Two such patients with advanced neoplastic disease who were undergoing treatment with IUdR or ICdR and who had not been vaccinated against smallpox for at least 20 years were vaccinated one hour after the first intravenous infusion was begun.
In each of these patients takes were not obtained while revaccination with the same amount of vaccine caused typical primary reaction in each subject subsequently. In two other patients receiving IUDR takes did occur. In a rabbit experiment there was a definite reduction of vaccinia titre in the treated animals as measured by the reaction to the intradermal inoculation, the degree of reduction was greater with increasing dosages of IUDR. This effect was noticed even when IUDR therapy was not initiated until 48 hours after inoculation. No toxic effects occurred in these animals. This work is currently in progress.

REFERENCES


2. Calabresi, P., McCollum, R. W. & Welch, A. D. (1963) Suppression of infections caused by a DNA-virus (vaccinia) in rabbits and man by the systemic administration of 5-Iodo-2'-deoxyuridine (Personal communication)