PRESENT DAY ANTI-VIRAL THERAPY IN DERMATOLOGY

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Summary

Attempts to develop drugs for the prevention and treatment of viral infections have faced with a variety of problems different from those encountered in the development of other type of antimicrobial agents. There are difficulties and consequently slow progress in the discovery of drugs which inhibit viral growth. Viruses have to strictly depend on living cells for replication. The narrow margin between the therapeutic dose of antiviral agents and lethal dose to the cells themselves is one of the major problems encountered in the development of viricidal drugs. Present day therapy in viral diseases is discussed in this paper with a review of the literature.

There are at present no standard methods for determining antiviral activity of a compound. Although the sensitivity of a bacterium to an antibiotic in vitro closely parallels the response to treatment in vivo, this association is not always true for viruses. It is well known that a great variety of the compounds that appear to be highly active against single or multiple viral agents in tissue cultures are without effects when applied to experimental infections in animals or naturally occurring ones in man. In this article an attempt has been made to discuss present day antiviral agents.

Methisazone

Benzaldehyde thiosemicarbazone was the first antiviral agent which was found effective in experimental viral infection[1]. Its derivative, 1-methylisatin-3 thiosemicarbazone (Methisazone, Marboran) was selected for therapy of human disease. It prevents the formation of complete viral particle by inhibiting late protein synthesis. It does not interfere with the production of viral components, but prevents their assembly into a complete virus[2]. It is effective against a number of poxviruses like those causing variola, variola minor, vaccinia, herpes simplex, foot and mouth disease and varicella. Despite its broad spectrum of activity in tissue culture, methisazone is effective in vivo mainly against the group of poxviruses only[3]. Methisazone has been primarily used for prevention of small pox and in the therapy of complications due to vaccinia. A trial of methisazone in the prophylaxis of small pox during an epidemic of the disease in Madras, produced an impressive effect by reducing the frequency of infection in those to whom it was given[4,5,6]. The dosage schedule varied from 1.5G daily[5] to 5G daily in 5 days[6]. Methisazone reduced the incidence of variola minor in contacts of small pox by 50% as compared to untreated persons[7]. The drug is useful in the treatment of two complications of small pox vaccination namely vaccinia gangrenosa and eczema vaccinatum[8]. A loading dose of 200 mg per Kg body weight followed by 8 doses

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Received for publication on 31—3—1978

of 400 mg/Kg every 6 hours is recommended. Drug is available in syrup and tablet forms. Maximum concentration is reached in the blood within 4 to 7 hours. There are no cumulative effects. Adverse effects are nausea and vomiting in 17 to 66%[9]. Alcohol should be avoided during therapy[9].

Idoxyuridine

The primary site of action of idoxyuridine (5-iodo-2-deoxyuridine, IDU, IUDR) has not been clearly defined[11]. It inhibits DNA formation by competing with its essential constituent - thymidine. The activity of idoxyuridine is limited to DNA viruses; primarily members of herpes virus group. It does not inhibit RNA viruses. The development of resistance of viruses to the drug both in vivo and vitro is common[12]. Idoxyuridine may be highly effective in the management of encephalitis and generalized infection caused by herpes hominis[12]. However failures have also been recorded[13]. It is impossible to draw any valid conclusions concerning the therapeutic effectiveness of idoxyuridine[14]. It is administered by continuous intravenous infusion to patients with encephalitis caused by herpes virus hominis. The recommended dose is 80–100 mg/Kg/day for 5 days. Most of the active form of the drug disappears from blood in about 30 minutes. A small amount is excreted in the urine. Adverse effects are, transient bone marrow depression, stomatitis, alopecia, hepatic injury, potential carcinogenicity and teratogenecity. Systemic administration is contraindicated in pregnancy and in diseases that are not potentially lethal.

Local application of IDU as a 5% suspension in dimethyl sulfoxide[15] (DMSO), or as 0.1% lotion or 0.5% cream in herpetic keratitis due to herpes simplex virus produced variable results [16,17,18,19,20]. Satisfactory responses were reported in case of herpes progenitalis in uncontrolled trials[21]. The drug has no effect in herpes zoster[22] or in warts where 1.5% strength was used under occlusion[23]. This lack of success is probably due to inability of the drug to penetrate epithelial cells.

Cytarabine

Cytarabine inhibits the synthesis of DNA. The activated spectrum is similiar to that of Idoxyuridine. Development of drug resistance has not been reported[24]. It is used topically in herpetic keratitis. It has been given systemically in cases of encephalitis and disseminated infection due to herpes virus hominis, and in infections caused by the varicella - Zoster virus with encouraging results[25]. One study has failed to reveal any therapeutic effect of this in herpes zoster[26]. The recommended dose is 40 mg per square meter for 5 days. The adverse effects are, immunosuppression, hepatic damage, G.I. disturbances, and bone marrow depression.

Cytarabine has several advantages over idoxyuridine such as, better action against herpes group especially Type 2 herpes virus, lack of development of resistance and non activation by deaminases in brain thus making it potentially more effective in the management of infections of central nervous system.

Photodynamic inactivation

The application of the photodynamic activity of certain heterocyclic dyes in the treatment of herpes simplex has provided a new approach towards therapy of this disease. It is a simple economical and yet fairly successful mode of therapy. Photodynamic inactivation of viruses in vitro was demonstrated in 1960[28]. Exposure of virus to solutions* of 0.1% proflavin, neutral

* The dye is dissolved in distilled water to make a concentration of 0.1% and sterilized by boiling in water bath for 10 minutes. Dyes are heat stable but unstable when exposed to light. Prepared solution must be kept in amber coloured bottles and stored at refrigerator temperature.

red methylene blue or toluidine blue results in the formation of a complex of the dye and viral nucleic acid. Minimal or no change in viral infectivity occurs in the dark. However 20 to 30 minutes after application, exposure to either fluorescent light at a close distance (15cms) for 15 minutes or to sunlight (proved better), leads to rapid deletion of the guanine moiety of the nucleic acid, resulting in loss of viral infectivity[29]. Treatment can be carried out at home by the patient. The procedure should be repeated several hours later. If no new lesions appear, there is no need for further treatment. If the disease recurs within 1 or 2 days after treatment, a second course of therapy should be given. Early treatment may abort the development of of vesiculation or abort the disease at the erythematous stage. Also, the duration of disease may be shortened or frequency of relapses decreased[28]. Adverse reactions are contact dermatitis and local irritation of the mucosal surfaces[14].

Griseofulvin

Griseofulvin is an antifungal antibiotic, but has been used with beneficial results in herpes zoster[30], lichen planus, herpes progenitalis[31], molluscum contagiosum[32,33] and warts[34]. Griseofulvin tends to concentrate more in the infected epidermis than in normal[35]. Antiviral action of griseofulvin may be due to interference with nucleic acid synthesis which in turn inhibit viral growth[10,30,31]. A dose of 250 mg of griseofulvin F.P. twice a day for 6 to 12 weeks were used without toxic effects in such cases. Photosensitivity has been reported[35] but not observed by many workers[30,31, 32,33,34,37,38]. Drug should be given immediately after a fatty meal.

Ether

Herpes simplex was treated with ether compresses with good results[39,40]. Fourteen cases of herpes simplex and herpes progenitalis treated with ether by the author are under observation for the last 18 to 24 months and not a single one has relapsed so far. It is postulated that the outer fatty covering of the virus is dissolved by the ether. A gauze piece soaked in ether is pressed on to the lesion for 5 minutes for 2 days. Since ether causes burning and smarting, xylocaine ointment should be rubbed over the lesion prior to the application of ether. In the presence of secondary infection, the infection is first treated with a suitable local and systemic antibiotic.

Interferons

These have not yet been proved to be clinically useful therapeutic agents. This is so because of their short half-life, after injection (10 minutes), and the fact that their species specificity limits large scale production. Only human cells can be used to produce interferons for the treatment of viral infections in man[14].

Acknowledgement

I am grateful to Colonel B. R. Bhatacharya, Officer Commanding, Command Hospital (WC), Chandigarh and Col. T. R. Chopra, Senior Adviser (Derm & Ven), Armed Forces (India) who have encouraged me to write this article.

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