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Virus chemotherapy: antiviral drugs and interferon*

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Summary

Early antiviral drugs, such as idoxuridine and vidarabine, are less effective than newer drugs, such as trifluorothymidine and acyclovir. However, trifluorothymidine is less subject to the development of drug-resistant strains and can be administered topically as a clear drop, which increases patient compliance. Acyclovir has low toxicity and is selective for virus-infected cells because it must be phosphorylated by the viral thymidine kinase to become active. However, drug-resistant strains are produced relatively easily in vitro and may also develop in man with long-term use. To date, no antiviral drug alone has been shown to be effective in the treatment of stromal disease, and no antiviral drug is able to eradicate virus latent in the ganglia and thereby prevent recurrent herpetic infections.

Combinations of antiviral drugs and antiviral drugs and interferon are being tested for enhanced efficacy in the treatment of ocular herpetic disease, and for prophylactic effects. The development of recombinant interferons has reduced cost and increased availability, but the effects of the 'manufactured' interferon are not identical to those of natural human leukocyte interferon in all experimental situations.

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Introduction

Since the development of the first useful antiviral drugs more than 20 years ago,

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there has been a constant and continuing effort to produce newer and more effective compounds for this purpose. Early drugs, such as idoxuridine [11] and vidarabine [19], provided therapy for virus infections that had previously been pharmacologically untreatable, but they had some drawbacks, chiefly insolubility and toxicity. Because of insolubility, these drugs must be applied topically in the eye as ointments, which blur vision and reduce compliance, and it is difficult to achieve therapeutic concentrations for cutaneous use. Systemic administration of vidarabine requires large volumes of fluid, and therefore can be carried out only intravenously in a hospital setting. Although clinical double-blind studies demonstrated that intravenously administered vidarabine had some effect on herpetic keratouveitis, i.e. reduced discomfort, anterior chamber reaction, and injection, the amount of fluid introduced over the seven-day treatment produced adverse reactions such as myalgia and lymphocytosis [1].

Both idoxuridine and vidarabine interfere with virus replication; however, they are not sufficiently selective for virus-infected cells to prevent toxic effects on non-infected, normal cells. Other problems include the development of virus strains resistant to the drugs (which is not uncommon with idoxuridine), lack of therapeutic effect on stromal herpetic disease, and inability to prevent recurrences of herpetic disease.

An ideal antiviral drug would have none of these defects; it would be soluble, selective, effective both therapeutically and prophylactically, and not subject to the development of virus resistance. Also, the ability to eradicate virus from the ganglia would eliminate the problem of recurrent disease caused by reactivation of the latent virus, although this is a distant goal at this time. Better drugs have become available since idoxuridine was introduced in 1962, but none meets all these criteria, and the search continues in many directions, including new compounds, combinations of existing compounds, and the use of both natural and recombinant interferon alone and in combination with antiviral drugs.

Trifluorothymidine

Efficacy against epithelial herpes

Trifluorothymidine is one of the newest drugs available for the topical treatment of ocular herpetic infections, and it is this author's (H.E.K.) drug of choice for the treatment of corneal epithelial herpes disease. It is highly soluble, and therefore can be administered as a drop that does not blur vision, so that compliance is enhanced. More importantly, trifluorothymidine is an extremely potent drug that appears to be more active than previous antiviral agents. Studies have shown that 97% of dendritic epithelial herpes lesions are healed by trifluorothymidine within 2 weeks, whereas only about 80% are cured by idoxuridine [26]. Although large geographic or ameboid ulcers heal somewhat more slowly than dendritic disease, a similar improvement in rate of healing is seen with trifluorothymidine, compared to earlier drugs [5].

Another advantage of this drug is the lack of resistant virus strains. Experimentally, it appears to be extremely difficult to produce virus strains resistant to this drug (A.B. Nesburn, pers. commun.), and to date, no resistant strains have been reported in human patients.

Treatment of stromal disease

However, as effective as trifluorothymidine is against epithelial herpetic disease, it appears to be useful in stromal disease only in the prevention of viral epithelial complications, and is not therapeutically effective for deep herpetic disease. Trifluorothymidine is used in conjunction with corticosteroids, which alleviate pain and swelling, to prevent a resurgence of epithelial disease, but it has not been shown to affect virus in the stroma in human eyes. Early treatment with trifluorothymidine in rabbits appears to inhibit the appearance of stromal disease [14,15] and trifluorothymidine and, even more so, bromovinyldeoxyuridine have been shown to be effective against experimental keratouveitis in rabbit eyes [15], but there are no human studies that demonstrate similar results, to our knowledge. Furthermore, trifluorothymidine cannot prevent recurrent disease, although it continues to be effective in treating subsequent episodes of recurrent herpes.

Acyclovir

Efficacy against epithelial herpes

One of the newest drugs with some potential for the treatment of ocular herpetic disease is acyclovir. This drug must be phosphorylated to be activated; the molecule is phosphorylated by the viral thymidine kinase enzyme but not by the cellular enzyme, so that the drug enters the metabolic chain of the virus-infected cells, and not the normal cells; therefore acyclovir is both highly selective [7] and relatively non-toxic.

Acyclovir is applied as an ointment, and so has the same compliance problems associated with idoxuridine and vidarabine. Although topical administration of acyclovir has been shown to be as effective as that of trifluorothymidine [13], there is no evidence that it is superior, and acyclovir has one major drawback that trifluorothymidine does not. It has been shown experimentally that virus strains resistant to acyclovir occur by deletion of the viral thymidine kinase or modification of the viral DNA polymerase and are easily produced in the laboratory [2], and there is considerable concern that similar, naturally-resistant strains will emerge with long-term usage.

Treatment of stromal disease

In the laboratory, it has been shown that topical or systemic administration of acyclovir before or within 24 h after infection with herpesvirus in rabbits prevents colonization of the ganglia [18]; however, this is not a practical approach in man. A combination of acyclovir and vidarabine appears to demonstrate enhanced efficacy in tissue culture (Hubbard, A.E. and Centifanto-Fitzgerald, Y.M., unpublished results) and prevents the development of stromal disease in rabbits [24], but no similar studies have been done in human patients. Administration of a combination of drugs may allow the use of lower doses of each drug, which would reduce the potential for development of resistant strains. Oral and topical acyclovir have been tested in a limited number of patients with disciform or necrotic stromal disease, but only minimal improvements in the amount of disease were seen (Sanitato et al., unpublis-

hed results). Further controlled studies in patients with only necrotic stromal disease are planned.

Treatment of recurrent disease

There was some hope that the low toxicity of acyclovir and related experimental compounds such as BVDU would make it possible to administer a safe oral dose that would prevent virus shedding and recurrent disease. However, experimental work in rabbits has demonstrated no effect on the clinical course of disease or the rate of recurrence [12]. Other investigators [16] have shown that virus cannot be isolated from the tears of rabbits receiving massive oral, topical and systemic doses of acyclovir in combination with experimental reactivation of virus by epinephrine iontophoresis; however, drug carry-over was not ruled out, and the very large amounts of drug used in this study are not practical for prophylactic use in humans (see Note added in proof).

Interferon

Investigations into the antiviral effect of interferon have been numerous, but difficult to compare because of a lack of standardized dosages and titers. In addition, such research has, until recently, been hampered by the scarcity and expense associated with obtaining natural human leukocyte interferon, which is produced by means of leukocytes from Finnish blood donors. Recently, interferon was subdivided into three classes: alpha, beta (fibroblast) and gamma (immune) interferon. Recent advances in recombinant DNA techniques have made it feasible to 'manufacture' recombinant interferons [17,20], and various subtypes of alpha and also beta interferon are now available. However, virtually all of the studies that compare recombinant and natural interferon show that they are not identical, and that their effects in different experimental situations vary.

Early work with interferon

Interferon has been tested against ocular herpetic infection since the early trial of Cantell and Tommila in 1960 [3]. It has been shown that once the virus disease is established, interferon has a definite, but weak effect. In owl monkeys, interferon is effective in preventing the appearance of herpetic keratitis [9], and this has suggested that prophylactic use might prevent recurrent herpetic disease. However, in a double-blind clinical trial, low titers of interferon were not effective in preventing recurrences [10], and the cost of obtaining sufficient quantities of high titer natural human leukocyte interferon has prevented further work in this area.

Human leukocyte interferon and antiviral drugs

Combinations of antiviral drugs and interferon have been tested and most have been more effective than either substance alone. Sundmacher et al. [23] showed that the combination of trifluorothymidine and interferon was more effective than trifluorothymidine alone, and De Koning et al. [6] confirmed these results. A recent clinical trial reported by Colin et al. [4] showed that the combination of interferon with

acyclovir was superior to acyclovir alone. However, in tissue culture and in animal studies, interferon and vidarabine were found to produce an antagonistic effect, and the resulting disease was increased in severity [25].

Recombinant interferon

Recombinant interferons are relatively inexpensive and available in large quantities, and can be, therefore, more easily utilized both in experimental studies and as therapeutic agents. However, it appears that the effects of recombinant interferons are not identical to those of natural human leukocyte interferon. Natural interferon has some effect in rabbits and in rabbit cell tissue culture, but the recombinant interferon had no effect under similar conditions. In monkeys, the recombinant interferon must be used before infection to produce an effect on herpes keratitis, while the natural substance has some ameliorating effect even when used after the disease has been established [22]. The prophylactic effects of recombinant and natural interferon, i.e. interferon administered before infection, are indistinguishable.

Note added in proof (received 7 July 1984)

A recently reported double-blind trial showed significantly fewer recurrences of genital herpes in patients receiving oral acyclovir, compared to those receiving placebo, over a 125-day period. The drug was well tolerated, but drug-resistant virus was isolated from acyclovir-treated patients who did have recurrences during the course of the study [27].

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