The impact of drug resistance upon virus chemotherapy

Since virus chemotherapy began, virologists have noted the ability of viruses to acquire resistance to inhibitors by mutation. This led to a pessimistic prediction of the likely success of antiviral drugs in man; an outlook partially justified by the finding that drug resistance to idoxuridine and adenine arabinoside occurred following topical therapy for herpes keratitis, in some cases causing problems in management of the disease (McGill & Scott, 1985).

Isolates of influenza resistant to rimantadine (Pemberton et al., 1986) and rhinoviruses resistant to picornavirus inhibitors (Al-Nakib, Yasin & Dearden, 1988) have also been obtained from human specimens. Laboratory studies confirmed that resistance in herpes simplex and varicella-zoster to nucleoside analogues and paramyxoviruses to specific inhibitors, in each case, can occur by means of a single base change in the virus nucleic acid by mutation, giving rise to a manifold reduction in sensitivity to the specific inhibitor. In several cases the identification of the precise genetic change by sequence analysis has been accomplished (Honess et al., 1984; Darby, Larder & Inglis, 1986; Kit et al., 1987) and the elucidation of such mutants can provide valuable insight into the mode of action of the drug, aiding the design of additional analogues with clinical potential. Furthermore the refractory nature of an infection from which a virus strain with biochemically proven resistance can be isolated may be taken as evidence for the specific mode of action of the drug in vivo. Thus viruses, having relatively high mutation rates and immense replication potential, would be expected to respond to widely-used inhibitors by the increasing emergence of drug-resistant strains in clinical practice.

To discover whether or not virus drug resistance has an overwhelming clinical impact would require the introduction of an efficacious drug for widespread use in man. The first of these was acyclovir. Despite the laboratory proven potential for acyclovir-resistant mutants to be selected, resistance has not been widely observed to date, although a few resistant mutants have been encountered in clinical practice (Barry, Lehman & Ellis, 1986; Collins & Oliver, 1986). The majority of clinical isolates remain sensitive to the drug when tested in tissue culture assays and this includes sequential isolates from patients receiving multiple and in some cases chronic therapy (Straus et al., 1984; Gold & Corey, 1987). Thus it appears that considerable constraints act upon herpes simplex virus populations which curtail the emergence of drug-resistant strains in the otherwise normal patient.

Acyclovir resistance in herpesviruses has generally been found to map to one or other of the thymidine kinase and the DNA-polynusidease loci (Coen & Schaffer, 1980). Moreover, some mutants apparently have reduced virulence compared with their parental strains, when tested in animal models (Field & Darby, 1980). This has been especially true for mutants that have absent or reduced ability to induce the enzyme thymidine kinase, which is instrumental in converting acyclovir to the nucleoside monophosphate allowing its subsequent conversion to the active nucleotide by cellular enzymes. Evidence has been obtained that mutants with altered DNA polymerase show reduced virulence in some cases (Field & Coen, 1986) and mutants that induce reduced or altered thymidine kinase also sometimes fall into this category. While it is relatively easy to induce mutants with reduced pathogenicity this certainly does not mean that particular mutants, retaining full pathogenic potential, cannot occur, albeit with relatively low frequency. There is laboratory evidence that even thymidine kinase-defective mutants may retain virulence (Izumi & Stevens, 1988). With time it is likely that such viruses will be observed more frequently in clinical practice.

While drug resistance in herpesviruses has not been a rapidly emerging problem in the general treatment of herpesvirus infections, this contrasts with the experience gained from treating the immunocompromised host. Indeed, the majority of resistant strains of herpes simplex and varicella zoster seen to date have been obtained from patients whose immunity is impaired. Such drug-resistant infections were first encountered in transplant recipients (Burns et al., 1982; Crumpacker et al., 1982; Wade et al., 1982; Parker et al., 1987). In some cases the viruses responsible appear to be less-pathogenic variants (Sibrack et al., 1982); opportunistic agents which thrive in the immunologically compromised patients. The greater extent of virus multiplication in these patients may be another factor in the selection of resistant strains, which occur with low frequency among virus progeny. It should also be noted that resistant isolates from clinical specimens may contain mixtures of resistant and sensitive virions (Christophers & Sutton, 1987). These problems are clearly not
confined to viruses, and novel drug-resistant variants of other microbes are emerging in this group of patients who are more permissive for attenuated variants. While drug resistance in transplant patients is well-documented, more recently the AIDS patient has been recognized as a new situation where herpes simplex virus drug resistance can emerge and cause intractable lesions (Erlich et al., 1989).

In the AIDS patient cytomegalovirus is a particularly important cause of disease and there is much interest in new forms of chemotherapy including ganciclovir (Morris, 1988). Ganciclovir is structurally related to acyclovir although with subtle differences in its mode of action (Biron et al. 1985). A human isolate of cytomegalovirus resistant to ganciclovir was partially characterized and shown to induce reduced levels of ganciclovir triphosphate in the infected cells (Biron et al., 1986) despite the fact that CMV does not itself encode a virus-specific thymidine kinase although it may modify the cellular function. In recent months there have been further reports of clinical resistance in cytomegalovirus (Erice et al., 1989) and there is every prospect that this will constitute an important bar to effective therapy.

It seems certain that virus drug resistance will generally continue to increase in importance. The phenomenon has been best studied in the herpesviruses but attention is now being paid to other families of viruses which are presently coming into the sphere of effective virus chemotherapy. With herpes the available data suggest that the importance of drug-resistance will only emerge very gradually; the experience with immunocompromised patients perhaps gives early warning of future problems which may be encountered more generally. At the moment immunocompromised patients represent a tiny proportion of the infected population and as such do not yet constitute a major source of resistant infections to others. The AIDS epidemic may alter this situation. Indeed, the development of azidothymidine resistance by the human immunodeficiency virus is predictable because of the need for chronic therapy in AIDS patients in the face of a persistent and immunologically damaging infection. The development of azidothymidine resistance in patients receiving therapy for periods in excess of six months has recently been confirmed beyond doubt (Larder, Darby & Richman, 1989).

The ability to detect the presence of resistant viruses in clinical practice is largely dependent upon the availability of convenient and reliable laboratory tests for drug sensitivity. Most experience to date relates to herpes simplex virus where a variety of test systems has been developed and used on a large scale. However, even for this well-studied virus, important questions remain to be answered relating to the possible shortcomings of various tissue culture methods (discussed by Field, 1988) and the suitability of alternative tests, for example, the direct measurement of thymidine kinase induction on freshly isolated virus plaques (Martin et al., 1985). There are still doubts about the relative ability of all these tests to detect resistant strains adequately, perhaps as minor components of heterogeneous virus populations. Animal models exist in which drug-resistance development both in normal (Field, 1982) and immunocompromised hosts (Ellis et al., 1986) can be modelled, and methods for circumvention thus be approached. Furthermore, much work remains to be done before we can be really confident that the available laboratory methods are adequate to detect the presence (perhaps of minority populations) of resistant virus in clinical specimens and studies in this area are to be encouraged.

In summary, we should not be complacent about resistance in viruses. Experience with acyclovir and similar drugs has been very encouraging thus far in relation to the apparent low incidence of resistant strains (except in the immunocompromised patients), but there is a definite need for much more study in this area. There is still much more to be learnt about the mechanisms and importance of drug resistance in the already well-studied herpes simplex virus. We have much less knowledge of drug-resistance in other human herpes infections such as cytomegalovirus and other virus families, for example, orthomyxoviruses; as yet there is a paucity of information relating to drug resistance in those viruses of new importance in chemotherapy including rhinoviruses and especially the human immunodeficiency virus.

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References


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