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Acyclovir As A Public Health Hazard

The introduction of acyclovir (Zovirax) into the US market as a treatment of uncomplicated chickenpox represents an unprecedented step in the management of this most common of childhood illnesses. Chickenpox is caused by the varicella-zoster virus (VZV), one of six human herpesviruses, and it is estimated that approximately 97 percent of children will contract the illness before adolescence.[1] Varicella is among the most contagious of diseases. Recent evidence suggests that transmission occurs mainly through the skin lesions; one study found that there was a direct relation between number of skin lesions and spread to contacts.[2] It has also been noted that VZV can only rarely be cultured from the pharynx of index cases in outbreaks of chickenpox.[3] Complications, which include bacterial superinfection, thrombocytopenia, pneumonia, arthritis, hepatitis, and encephalitis, occur rarely in immunocompetent children. Nevertheless, the benign nature of the disease is transformed when an adolescent or adult is infected. Up to 33 percent of adults who develop chickenpox go on to develop varicella pneumonia,[4] resulting in significant morbidity and mortality.

After primary infection, the virus enters a latent phase in the dorsal root ganglia for the life of the host. In approximately 50 percent of the population, an event, probably an attenuation of cellular immunity, will reactivate the virus, causing herpes zoster, a condition that often results

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in significant morbidity.[4] Immunity to VZV appears to consist of both cell-mediated and humoral immunity components, and studies of VZV vaccinees have suggested that the risk of subsequent development of herpes zoster is inversely related to the strength of the cell-mediated immune response. Interestingly, the humoral immune response has no such predictive value.[5]

The host immune system appears to respond differently to primary infection with the virus at various stages of development. In pregnancy, the virus has been firmly established as being teratogenic. The profound manifestations and disseminated infection of VZV in utero are thought to be secondary to the inability of the fetal immune system to mount a cell-mediated response to the virus.[6]

In young children, a broad cell-mediated and humoral immune response is observed in response to both natural infection and vaccination with attenuated VZV.[7,8] Nonimmune adults vaccinated with live attenuated VZV, on the other hand, often develop only partial, short-lived immunity, suggesting that they have an impaired ability to mount an immune response against VZV.[9] Perhaps there is an immunologic "window of opportunity," after which primary infection fails to elicit effective protection. Antigen load also appears to be an important determinant of duration of immune response. Subjects given low doses of VZV vaccine showed initial seroconversion but subsequent diminution of cell-mediated immunity after 1 year, as opposed to those who were given higher antigen loads.[10]

In an article in *The New England Journal of Medicine*, Dunkle, et al.,[11] pronounced acyclovir to be safe and effective for the treatment of uncomplicated varicella in immunocompetent children. They randomized 724 children to receive acyclovir or placebo for 5 days. From a clinical standpoint, therapeutic benefit was modest as measured by duration of fever and constitutional symptoms, number of lesions, and pruritus. Importantly, there was no evidence that acyclovir had any effect on the rate of complications of varicella. Indeed, the benign nature of the disease was underscored, as the only subject in the study to develop a serious complication (cerebellar ataxia in a placebo recipient) experienced resolution after 36 hours without treatment in the hospital.

Perhaps the most important drawback of the study was that the only attempt made to determine the immune response to treatment was measuring the level of antibody directed against VZV membrane antigen, measuring the presumed humoral immunity. The authors chose to ignore measurements of cell-mediated immunity, despite evidence that humoral immunity alone could be insufficient to protect against primary varicella or herpes zoster.[12,13] Additionally, any meaningful predictions of the long-term effect of treatment with acyclovir would have to be based on measurements of (at least) T lymphocytes responsible for retaining memory of the VZV antigen. Instead, the authors speculated that it was not likely that treatment with acyclovir would predispose to future reinfection with VZV or increase the rate of herpes zoster.

If the history of medicine in the realm of treatment and prevention of endemic diseases has taught us a valuable lesson, it should be that extraordinary caution is needed when dealing with such a ubiquitous virus. Despite the triumph over smallpox, all of the other common childhood illnesses remain with us to a greater or lesser degree. Vaccine failures have spectacularly dashed early hopes to control rubella and eliminate measles by shifting the age of infection to adolescence and adulthood. In the case of varicella, eradication of the disease is not feasible, because we are all carriers of the virus, and half of us shed it at some time during our lives during episodes of herpes zoster. It is conceivable that treatment with acyclovir during primary infection could reduce the antigen load faced by the body's immune system, thereby rendering the patient susceptible to future reinfection or recrudescence at an age when complications are far more common and severe. Obviously, the price of having even 1 percent of the population develop incomplete or altered immunity to VZV would be immense. In addition, the decrease in the number of skin lesions with treatment could limit spread of infection, thereby increasing the chance that contacts will miss being infected at an optimum age. Consider further the expense of the drug itself at a time when physicians are coming under increasing pressure to justify the cost of therapy.

Aggressive marketing of acyclovir for treatment of uncomplicated chickenpox probably will

have a powerful effect on prescribing practices of physicians during an outbreak of varicella in the community. Demand for the new medicine is likely to be great, and the potential for abuse, high.

Concerned families are likely to request the medication prophylactically for household contacts, and physicians could feel obliged to prescribe acyclovir for undifferentiated fevers during a chickenpox outbreak. Patients and physicians alike could be under the impression that the medication reduces the rate of complications, leading to the notion that acyclovir is the standard of care for this condition.

It is often difficult for physicians to resist the use of a medication when we have a disease process that might be ameliorated by its use. Sometimes, however, the disadvantages of therapy outweigh the good these drugs can do. Certainly, without further careful study, the widespread treatment of a ubiquitous and overwhelmingly benign disease with a costly drug of marginal clinical benefit and unknown long-term effects is probably unwarranted. The best treatment of varicella might remain the venerable practice of ensuring exposure to infection at an appropriately early age.

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