Personal Practice

Acyclovir Therapy in Chickenpox

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Chickenpox is a common infectious viral disease of childhood which engages limited attention of the public as well as medical profession due to a relatively brief and self limiting course. Until more than a decade ago, pharmacological intervention for this malady was neither available nor advocated. However, the advent of a safe antiviral drug, acyclovir, with a documented efficacy in immuno-compromised children with chickenpox, has fuelled an intense debate regarding the need and justification of recommending this drug routinely, even in immuno-competent subjects with the disease. The present communication is intended to analyze some of the pertinent issues in this context, in the light of available scientific evidence.

Magnitude of Problem

The lack of an effective reporting system and the invariably mild and self limiting nature of illness precludes the availability of reliable national community based data on the prevalence or annual incidence of the disease in the country. Estimates indicate that in USA, chickenpox accounts for nearly 3 million cases and 6000 hospital admissions, annually(l). In a recent study(2), 8823 admissions due to chickenpox were documented over a period of 9 years (1987 to 1995) at the Infectious Disease Hospital in Delhi. Accounting for the population dimension and the fact that only the severe or complicated cases are hospitalized, the projected magnitude of the problem in India is likely to be substantially greater.

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Clinical Spectrum and the Need for Treatment

Although generally considered to be benign, the disease is sometimes associated with significant complications, which may even be life threatening, especially in immuno-compromised individuals. Chicken-pox and its complications have been reported to account for about 56 hospitalizations per 1000,000 person years in under 10 years age group in USA(3). With the recognition of the association of aspirin ingestion and Reye's syndrome in children with chickenpox, deaths due to this entity in immuno-competent children have become quite rare(4). Skin infections due to *S. aureus* or S. *pyogenes* are the most common complications of varicella. Cellulitis, lymphadenitis, subcutaneous abscesses, arthritis and osteomyelitis may occur due to local spread or transient bacteremia. Varicella gangrenosa and acute bacterial sepsis are rare but potentially life threatening complications. Bacterial super infections, varicella encephalitis and varicella pneumonia have been reported as the most common complications, necessitating hospitalization, accounting for 9, 9 and 6 hospitalizations per million population per year respectively, in children up to 10 years

of age(3). Cerebellar ataxia, hepatitis, acute thrombocytopenia, nephritis, nephrotic syndrome, hemolytic uremic syndrome, myocarditis, pericarditis, pancreatitis and orchitis have sometimes been seen even in immuno-competent children(5).

Apart from aforementioned complications, the immuno-compromised children, newborn infants or healthy adolescents may occasionally develop severe and progressive varicella infection with pneumonia and respiratory failure, hepatitis, encephalitis, disseminated intravascular coagulation and syndrome of inappropriate anti-diuretic hormone secretion with attendant mortality (5).

From the foregoing, it is evident that chickenpox is not entirely a benign entity. Safe and effective treatment is especially desirable for those at risk for serious disease or with complications.

Acyclovir Therapy

Acyclovir is a synthetic purine nucleoside analogue with *in vitro* activity against the *Herpes simplex, Epstein ban* and *Varicella zoster* viruses(6). The viral thymidine kinase converts acyclovir intracellularly to it's active triphosphate form, which inhibits DNA polymerase enzyme and prevents viral DNA synthesis, though other relatively less well defined mechanisms may also be involved(7).

The drug has been shown to be significantly effective in reducing the incidence of life threatening infections and hasten recovery in immuno-compromised children with chickenpox(8,9). Acyclovir is, therefore, recommended in all children with congenital (particularly cell mediated) or acquired immunodeficiency disorders. Neonatal varicella after maternal varicella within 5 days before or two days after delivery, and severe or complicated varicella infections (associated with pneumonia or encephalitis) also necessitate prompt treatment with intravenous acyclovir, in a similar manner(5). The drug dosage, duration and route of administration of acyclovir, for severe infections or immuno-suppressed hosts are summarized in *Table I.*

The side effects of intravenous acyclovir administration are mainly local and include pain, inflammation and phlebitis at the site of injection. Renal impairment, megaloblastic anemia, hepatic and neurologic dysfunction (tremors, confusion, lethargy and seizures) are infrequent side effects of intravenous acyclovir(l0).

Routine Acyclovir Therapy

The need and justification of recommending routine acyclovir therapy in otherwise healthy children with chickenpox is highly controversial. The various pros and cons for adopting such a practice are summarized below.

Justification For

The most promising argument in favor of routine use of acyclovir in immuno-competent children with chickenpox is the propounded, "rapid" attenuation of the "misery index" of chickenpox for the patient and family by acyclovir(ll). The drug, taken orally, has been shown to significantly reduce the number of lesions, duration of new lesion formation (and thus lessen chances of facial scarring) and severity of illness; and accelerate progression towards healing with less itching and fewer residual hypopigmented lesions(l,12,13,14). On the whole the reduction in duration of fever or time to recovery by about 1 day, may result in slightly earlier return of child to school and parents to work(12). Most trials have emphasized the importance of administraion of the drug in the first 24 hours of appearance of rash, which may be difficult to

accomplish in actual practice. However, in a recent report from Italy, no significant difference was found in the efficacy of drug when administered within or after first 24 hours(14). Oral administration of acyclovir in the recommended schedule, in otherwise healthy children with chickenpox *(Table 1),* is virtually devoid of significant adverse effects apart from minor gastrointestinal complaints.

Arguments Against

The major limitation of use of acyclovir is it's inability to prevent the complications and secondary spread of chickenpox(15), making it unsuitable for preventing epidemic spread in community, especially in schools. Further, the expected clinical benefit in an uncomplicated case of chickenpox is *marginal* (reduction by only a day).

Concerns have also been expressed regarding the possibility of promoting resistance of the virus to acyclovir and increased risk or early occurrence of reactivation disease (Herpes zoster) in the treated children(15). There is no evidence at present to suggest that resistant strains of varicella virus will occur in the immuno-competent community with routine antiviral use. Resistance has rarely occurred in immuno-compromised patients with *Varicella zoster* virus infection; prolonged viral replication in these patients provides an optimum environment for selection of resistant strains, but these strains have not been shown to be transmissible, as yet(16). Untreated immuno-competent patients shut off the replication of *Varicella zoster* virus by about the third day of rash, making it improbable that any infectious *Varicella zoster,* whether sensitive or resistant, would persist in the face of a normal immune system (16). Studies of the anti-

TABLE I- Acyclovir Therapy in Chickenpox

Immunosuppressed	Otherwise Healthy Children *(Routine use controversial)*
Dose:	Dose:
< 1 yr: 10mg/kg/dose, 8 hourly, as 1h intravenous infusion	20 mg/kg/dose (maximum 800 mg/ dose), 6 hourly daily, orally
> 1 yr: 500 mg/ m^2/ dose, 8 hourly, as 1h intravenous infusion	
Initiation timings:	Initiation Timing:
As soon as possible after initial lesion appears	Preferably within 24hrs after initial lesion appears
Duration:	Duration:
7 days or until no new lesions have appeared for 48 h.	5 days

body titers after acyclovir treatment in childhood chickenpox indicate that the humoral immunological response is unmodified at 28 days and 1 year(17). Acyclovir probably does not have a measurable effect on the immunity because the viremia precedes the therapy by several days, allowing sufficient antigenic stimulation to provide durable active immunity(18). Furthermore, since acyclovir treatment interferes with neither the pre-emption patho-physiology of

primary *Varicella zoster* virus infection nor the subsequent immune response, treatment of chickenpox is not likely to predispose the host to re-infection or to a higher risk of reactivation disease(19).

Cost benefit analysis is an important aspect for formulating recommendations. In India, currently the average cost of a 5 day course of acyclovir in 2-5 years old children is likely to range from Rs 400/- to 700/-*(Table II).* The equivalent cost in U.K. has been estimated to be at least 32 Pounds(4). Obviously, the cost of routine therapy is substantial by any standards and the potential economic benefits of earlier return to work of parents seem unlikely to offset the enormous cost of the drugs and medical consultation(4).

The medico-legal implications (especially when complications develop) of adopting acyclovir therapy in chickenpox as a standard of care also need to be considered, in view of lack of existence of a definite evidence of reduction in rates of complications with therapy(15).

Possible Balance

Considering the various pros and cons, even the developed countries are currently reluctant to recommend routine acyclovir therapy in otherwise healthy children with chickenpox. Although there is negligible scientific data to support the recommendation, it may be worthwhile to administer acyclovir to immuno-competent children with chronic cutaneous disorders and diseases which may be exacerbated by acute varicella infection (like diabetes mellitus and cystic fibrosis), or the subjects on intermittent steroid therapy(5). Similarly, the disease is much more severe in adolescents and young adults as compared to younger children. Secondary cases within a family are also likely to suffer a more severe disease owing to larger viral innoculum. Thus, adolescents and secondary cases (preferably intra-familial) could be the potential subgroups for offering treatment with acyclovir(4), if affordable.

TABLE II- *Commercially Available Preparations of Oral Acyclovir*

Trade name	Cost (Rs.)
Cyclovir (Cadila H.C.)	19.90
Herpex (Torrent)	21.00
Herperax (Micronova)	18.00
Zovirax (Wellcome)	30.00

The available strength of all preparations is 200 mg.

Prophylactic Acyclovir Therapy

Clinical evidence as yet does not indicate that acyclovir can prevent chickenpox. It would be difficult to ascertain whether acyclovir prophylaxis resulted in sub-clinical case of chickenpox or whether the exposure was trivial. Without this knowledge, the patient will need to receive prophylaxis after every subsequent exposure, Prophylaxis could leave a patient with imperfect immunity and susceptible to chickenpox later in life when the disease can be more serious(ll). It would, therefore, be better to allow chickenpox to manifest itself and then treat (if required) immediately (i.e., within 24 hours of appearance of rash), thus ensuring a durable immune response.

Conclusion

The utility of prompt, parenteral administration of acyclovir in severe life threatening varicella infections, especially in immuno-compromised children and neonates is undisputed. Oral acyclovir is a safe and effective mode of therapy for otherwise healthy children with uncomplicated chickenpox, when started within 24 hours of appearance of the rash. However, in view of its

substantial cost, marginal clinical benefit and ineffectiveness in preventing complications and secondary spread, the drug cannot be recommended routinely in all healthy children with chickenpox. Currently, at best, selective use could be considered in healthy adolescents and secondary intra-familial cases, wherever affordable.

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