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Clinical use of acyclovir

Acyclovir is a potent, specific antiviral drug of remarkably low apparent toxicity which is active against herpes simplex viruses types I and II and varicella zoster virus. It is now available in Britain as ophthalmic ointment, skin cream, and oral and intravenous formulations. A leading article by Professor Morag Timbury summarised its mode of action and the results of early clinical trials.[1] Further work has confirmed the value of this drug in the prophylaxis and treatment of severe and life threatening infections.

The development of acyclovir shows the possibility of finding specific virus targets for antiviral compounds. Modification of its acyclic nucleoside structure may produce further useful drugs—but we have no reason to expect an influx of new therapeutic agents with different mechanisms of action during virus replication. Although at present there is little evidence that resistance is easily generated in vivo, if it were to become widespread we might be forced to return to using the less effective, non-specific cytotoxic drugs for herpes infections. The time has come, therefore, to consider the potential uses of acyclovir and possibly to question whether it should be used indiscriminately for minor, self limiting infections.

Herpes simplex viruses types I and II and varicella zoster virus establish latent infections, and most adults are infected with at least one of them. Both primary and recurrent disease usually result in the formation of vesicles and ulcers on the skin or mucous membranes or both. Acyclovir acts through virus coded enzymes and may be expected to affect only the development of early lesions or the spread of viruses from cell to cell. It cannot reasonably be expected to influence wound healing, when the maximal effect of viral replication has been reached, or to have any effect on late sequelae such as nerve palsies. As a general rule the earlier treatment begins the more likelihood there is of influencing the disease. Many patients present too late to be amenable to treatment.

The management of ocular herpes simplex virus infection has been remarkably improved by topical antiviral drugs. Acyclovir is at least as effective as idoxuridine,[2] vidarabine,[3] and trifluorothymidine,[4] and it produces faster healing.

Individuals vary considerably in their response to genital herpes simplex virus infection. The primary disease may sometimes be severe and prolonged and may require treatment with intravenous or oral acyclovir. Several trials have shown a reduction of pain and other symptoms and of virus shedding and accelerated healing.[5-8] Despite early hopes treatment of primary herpes simplex virus infection has not been shown to influence latency or subsequent recurrence. Recurrent attacks are normally less severe and of much shorter duration than primary disease. The duration of symptoms may be somewhat reduced when acyclovir cream is applied very early, but the benefits are marginal.[9] Once vesicles or ulcers are visible the patient is unlikely to benefit from acyclovir in any form, and it should not be used. A few patients suffer from frequent recurrences, and some are rarely free of lesions. Acyclovir has been found to suppress attacks when it is used continuously, though when treatment stops recurrences usually return to the original rate.[10-12] No serious side effects have emerged during trials of suppressive treatment, but the long term safety of the drug needs further evaluation. Suppression of attacks by intermittent or continuous administration may be justified in the most severely affected.

Cold sores (herpes labialis) are common, they are rarely severe, and scarring is unusual. Accelerated healing (from six to four days) has been reported in a trial of acyclovir cream when the application started before lesions were visible.[13] The constant worry of creating resistant strains makes it doubtful whether treatment is justified for this marginal effect in those with mild lesions. Primary or recurrent skin lesions may require topical or oral treatment, particularly if they are close to the eye (for example, "scrum pox" in rugby players[14]) or are likely to result in prolonged disability (for example, herpetic whitlow).

The mean case fatality of untreated herpes simplex virus encephalitis is 70%, and severe brain damage is common in survivors. Sköldenberg and colleagues have recently shown that mortality was cut when intravenous acyclovir was compared with vidarabine (19% versus 50%).[15] Long term sequelae were also reduced. Nicholson has sensibly recommended that when a presumptive diagnosis of herpes virus encephalitis is made intravenous acyclovir should be started immediately and continued for 10 days or until another diagnosis is reached.[16] Attempts to confirm the diagnosis by serology should follow.

If immunocompromised patients develop herpes simplex virus lesions they are likely to have prolonged local disease—or to develop viraemia and disseminated infection. Clinical trials have shown the value of acyclovir in controlling these infections, and prompt treatment with the oral or intravenous drug is indicated.[17] When given prophylactically acyclovir effectively suppresses herpes simplex virus infec-

tions. This has been particularly important in recipients of bone marrow transplants.[18 19]

Neonatal herpes simplex infection is very rare in Britain. Vidarabine has some effect,[20] and early reports of acyclovir treatment are encouraging. More data are necessary, but acyclovir, which is known to be well tolerated in babies, may prove to be the drug of choice.[21]

Varicella zoster virus is less sensitive to acyclovir than herpes simplex virus, but adequate therapeutic concentrations can be reached by intravenous treatment.

There is no question of the value of acyclovir in the treatment of herpes zoster in the immunocompromised.[22] Some benefit has been seen in the treatment of zoster in normal people, but the expense of treatment and inconvenience of intravenous administration may limit its use.[23 24] There may be a case for early treatment in severe trigeminal zoster if desquamation is likely to be extensive. McKendrick and colleagues have recently reported successful reductions in duration of vesicles and pain and accelerated healing in patients given oral acyclovir.[25] If these preliminary results are confirmed early treatment of zoster in general practice should be possible. None of the trials of acyclovir to date have shown a useful effect on postherpetic neuralgia.

In summary, acyclovir is sufficiently potent and non-toxic to use in any severe or life threatening condition caused by herpes simplex viruses I and II and varicella zoster virus. In less severe and recurrent disease it seems sensible to limit its use, as indiscriminate prescribing may lead to increasing resistance and loss of efficacy of a lifesaving drug.

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Care of the acutely injured hand

Hand injuries account for one third of all accidents at work.[1] Domestic hand injuries make up one third of the total (J Michon, data presented at the 10th International Meeting of Microsurgery, Strasburg, 1984). They are enormously costly, to both the individual and the economy because of time lost from work, financial compensation, and disability. Most are avoidable; much effort should be directed towards prevention through educational programmes in the factory and the home.[2]

Primary management has great influence on the extent of the eventual functional recovery.[3] Above all the injury must not be exacerbated or complicated. Hand injuries are rarely, if ever, life threatening. Haemorrhage may be a problem, but it is usually transitory and controllable by raising the hand and applying a padded pressure dressing. A tourniquet should never be used. The possibility of concomitant serious injury must be excluded before detailed examination and treatment of the hand.

The history should contain personal details of the patient which will influence treatment, such as age, sex, right or left handedness, occupation, hobbies, general health, and ability to cooperate with rehabilitation. Detailed information about the precise mechanism of injury should be recorded. This will indicate whether the tissues have been cut, crushed, avulsed, degloved, or burnt. Common patterns of injury should be known—for example, extensive internal damage with only a small skin laceration in glass injuries and fractures associated with crushing; in such cases the surgeon will have some idea of the structures likely to be affected.

Examination should be expeditious and cause no additional discomfort. Five questions should be answered. Is the viability of the hand or digit in doubt? Although this may be difficult to assess before normal anatomical relations are restored, avascularity is suggested by pale, cold skin with slow or absent capillary refill, particularly noticeable at the nail bed. Is the skeleton stable? Instability may be obvious in severe injuries, but good quality radiographs in at least two planes should always be obtained.

Is there actual or impending skin loss? Appearances are deceptive: the nature of the accident is perhaps the most reliable guide. Shearing injuries always produce undermining and eventual tissue necrosis. Is there evidence of sensory or motor loss indicating nerve injury? The most reliable sign of sensory damage is loss of sweating in the nerve territory. This is immediately positive after division of the nerve and is easily shown by loss of tactile adherence when a plastic pen is lightly drawn over the affected area.[4] Pinprick is a crude and unreliable test. Individual muscle testing will show evidence of motor paralysis. Is there evidence of tendon damage? This produces an imbalance in resting tone and so abnormal posture. It is further shown by a tenodesis test—that is, in the normal relaxed hand the fingers fall into an arcade of flexion when the wrist is passively extended and extend when the wrist is flexed. The relation of each finger to the next will be disturbed if tendons are divided.

Having attempted to answer these questions, it should be remembered that the true extent of damage may be much greater than that found by clinical examination; in penetrating injuries with sharp objects the definitive examination is surgical exploration. Indeed, repair necessitates thorough wound exploration by an experienced surgeon with fine