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The potential of phosphonofomate for the treatment of herpes simplex labialis

Herpes simplex labialis or cold sores is the most common disease in man caused by HSV type I. The infection is often recurrent, representing reactivation of latent virus residing in the trigeminal ganglion. It has been estimated that 7% of the population of the USA has more than two episodes of recurrent HSL per year (Overall, 1979). In epidemiological terms this is an important uncontrolled infection, while in terms of the clinical use of antiviral drugs the infection represents an ideal target where compounds can be used topically. It is rather surprising then that more attention has not been directed in the past towards this troublesome disease. This situation may now change dramatically with the advent of a simple molecule sodium phosphonofomate (Helgstrand et al., 1978). This compound is related to the parent phosphonoacetic acid (Shipkowits et al., 1973) but has the advantage of non-toxicity following application on the skin. In addition phosphonofomate (PFA) has a rather different antiviral spectrum: as well as anti herpes type I and II activity PFA inhibits DNA polymerase of hepatitis B virus (Nordenfelt, Helgstrand & Oberg, 1979). Careful laboratory studies have established that PFA inhibits the DNA polymerase of HSV-1 and HSV-2 viruses, possibly by acting as a non-competitive inhibitor at the pyrophosphate binding site on the enzyme itself. Work in animal model infections, particularly infection of guinea pig skin, has established a marked therapeutic activity of PFA (Alenius, Dinter & Oberg, 1978). In this model infection a depilated area of the skin is punctured lightly with a gun and infected with HSV-1 and 24 h later an erythema is detected. Addition of 2% PFA as a topical cream six times daily thereafter results in a marked therapeutic activity both measured as a cumulative score and on a time to healing parameter. Other compounds such as idoxuridine ribavirin, acyclovir, cytosine arabinoside are less effective in this model system (reviewed by Collier & Oxford, 1980).

A relevant observation of these studies is that the vehicle or ointment used to apply the antiviral compound is of considerable importance, and more attention is needed on parameters of drug adsorption and solubility. Preliminary clinical trials reported at the antiviral meetings at the London Hospital in November 1979 and in Atlanta in March 1980 have described a therapeutic effect of PFA in man. The therapeutic efficacy of 3% ointment used six times daily for 4 days was studied in a multicentre double blind, placebo controlled trial in patients with a history of recurrent herpes labialis (Wallin, Lernestedt & Lycke, 1980). Two-hundred episodes of current disease have been studied to date. At the time of the first episode the patient was randomly assigned to the control or active treatment group. At the first episode treatment was begun within 24 h whereas after cross over and with the next episode the patients used self-medication immediately clinical signs were obvious. At the first episode lesion size and stage were measured at the clinic and, in addition, each patient kept a record of pain score and lesion development. PFA significantly shortened the papular and vesicular stages of the disease and significantly more patients in the control group developed new vesicles. Of particular interest for future clinical trials, it was noted that many patients were 'well able to discriminate between active and placebo treatment in spite of a high comparability of objective measurements'. In short, patients derived a beneficial effect from treatment—a consideration easily overlooked in initial double blind scientifically controlled trials! Obviously these trials will have to be confirmed, but at this stage the data appear rather convincing. A cloud on the horizon concerns the ability of absorbed PFA to bind tightly, but not irreversibly, to the inorganic matrix of bone. To date no adverse toxicological effects of this binding has been noted in animal models. Of course tetracyclines bind rather strongly to certain bone tissues but this has not obstructed unduly the therapeutic use of this group of compounds. Acyclovir, another anti-HSV compound acting also as an inhibitor of HSV DNA polymerase (Schaeffer et al., 1978) is now undergoing extensive clinical trials with herpes encephalitis, genitalis and labialis. Without being too pessimistic one should note that drug resistant herpes virus mutants to both compounds can be obtained with relative ease, including strains resistant to both ACV and PFA and the possible emergence of such viruses is being carefully monitored in clinical trials. Both compounds are relatively cheap and easy to manufacture.
and with amantadine may represent the first trio of widely used antivirals.

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References


The treatment of brucellosis

In Britain human brucellosis is caused by Brucella abortus and is associated with occupational contact with infected cattle, and less frequently with infected milk or cream. Brucella melitensis infections are seen but invariably these infections have been contracted abroad. As the eradication programme of bovine brucellosis has been extended to all parts of the country the incidence of human brucellosis has declined, and it is likely that in the 1980s only small numbers of infections will be seen. Therefore it is an opportune time to examine the therapeutic agents that have been used in the treatment of brucellosis and to assess their efficacy.

In both its acute and chronic form it is essentially a disease of intracellular parasitism. A satisfactory response to treatment is dependent on the elimination of intracellular organisms (Magoffin & Spink, 1951) either by the use of antibacterial agents that penetrate the infected cells or by maintaining high extracellular levels for an extended period of time.

Because of the insidious onset and the variable manifestations of the disease many ill defined fevers are easily attributed to brucellosis in patients with serum antibodies due to past infection from occupational contact. Consequently this uncertainty makes evaluation of treatment difficult and may account for the use of a succession of antibacterial agents as they become available.

Tetracyclines have been used for many years and are effective agents in the treatment of brucella infections (Spink, 1964; Rizzo-Naudi, Grisetti-Soler & Ganado, 1967). Spink (1956) reported on the treatment of 67 patients with acute brucellosis with 500 mg of tetracycline four times a day for 10 days to 21 days. Forty-eight patients recovered promptly after the initial course of treatment and 11 of 19 patients who relapsed responded to a further course of treatment. Rizzo-Naudi et al., (1967) reported similar findings after treating 400 Br. melitensis infections with tetracycline, they recommend that tetracycline should be given for at least 21 days.

One of us (L.R.) has treated more than 30 cases of acute brucellosis with three courses of tetracycline, a course consisted of 1 g of tetracycline twice a day for 4 weeks with an interval of 4 weeks without treatment between each course. No relapses were seen after this prolonged treatment. Farrell, Hinchliffe & Robertson (1976) compared the in-vitro sensitivity of brucellae to tetracycline and its analogues. The mean minimal inhibitory concentrations (MICs) for demethylchlortetracycline, doxycycline, lymecycline and tetracycline were < 1 mg/l.

It is difficult to select any one of this group as the best for clinical use: lymecycline has not had extensive clinical trials, and the reported incidence of photosensitization and gastrointestinal disturbances associated with demethylchlortetracycline may be a dis-