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Interfering with the real cold

Intranasal sprays of interferons are effective in volunteers in preventing experimental colds due to rhinoviruses, but they have no appreciable benefit when given after the symptoms have begun. The prophylactic effect is more potent than that of any of the specific antirhinovirus drugs which have been tested at the Medical Research Council Common Cold Unit.[1]

If long term treatment with interferon is given to prevent natural colds, after about two weeks many volunteers develop local nasal discomfort with stuffiness, dryness, crusting, and discharge of blood tinged mucus.[2-4] These features coincide with inflammatory changes in the nasal mucosa with superficial ulceration and a dense lymphocytic infiltrate.[5] Neither the symptoms nor the microscopic changes are like natural colds—but perhaps they are not surprising in view of the fever and influenza-like symptoms which occur in patients given interferon parenterally and the local inflammation in those given it intradermally. These effects are probably caused, at least in part, by the induction of inflammatory prostaglandin synthesis. Interferon given intranasally may be absorbed, as evidenced by a fall in the circulating lymphocyte count and minor general symptoms in a few volunteers, but whether absorption is enhanced when the mucosa is inflamed is not known. In practical terms long term treatment with intranasal interferon seems not be tolerated by about half the recipients, and the changes induced in the nasal mucosa may prove unacceptable even in those without symptoms.

Since, however, side effects occur after about two weeks' treatment with interferon and colds can effectively be prevented by shorter courses, the logical time to take interferon would be immediately after close contact with a cold. Mounting a trial to test the effectiveness of interferon in these circumstances might seem a daunting task. Colds probably circulate most efficiently among young children in close contact with each other in school, and they often then pass on the infection to adults at home.[6] The family has therefore been the setting for several postexposure prophylaxis studies comparing intranasal interferon with placebo sprays under double blind conditions. Colds were assessed from daily symptom record cards, physician and nurse evaluation, the results of virus culture, and by finding rising antibody titres. Only limited details of the first study (and no data on virus isolation) were published, but the results did suggest a reduction in the number of days that recipients of recombinant interferon (IFL-rA, Hoffmann-La Roche) had nasal symptoms compared with recipients of placebo.[7] Two once daily regimens of interferon were tested and, although the lower dose (3×10^5 U) would not have been expected to prevent experimental colds, the effects were comparable in both treatment groups.

More recently, larger studies from Australia and the United States using almost identical protocols have given remarkably similar results.[8,9] Families were recruited into both studies prospectively and allocated at random either to recombinant interferon (IFN-alpha$_2$, Schering Corporation, 5×10^6 U once daily) or to placebo nasal sprays. Within 48 hours of one family member developing upper respiratory symptoms, all the others over 14 years of age started the prescribed treatment and continued for one week. The same treatment was taken for each event throughout the study period. Only the results of early prophylaxis using completed courses of treatment to protect against definite colds in the index case were analysed.

In these two trials, 22 and 23 clinical colds were reported per 100 courses of placebo taken; 16 and 14 colds respectively were reported per 100 courses of interferon, and the colds which did develop in the patients given interferon were less severe. Specimens for virus isolation were not obtained from all the patients with clinical colds, and the rhinovirus isolation rate was lower than might have been expected, perhaps because nasal washings were not done.[6,10] Nevertheless, if a definite rhinovirus cold developed in the index case, the risk of a recipient of interferon contracting a rhinovirus cold was much reduced. In contrast, recipients of interferon developed proved infections with *Mycoplasma pneumoniae*, parainfluenza, influenza, or coronaviruses just as often as recipients of placebo. The latter two of these illnesses may be inhibited by prophylactic interferon in volunteers under controlled conditions,[11-13] so perhaps interferon was not started early enough or in optimal dosage. More frequent dosing, especially in the early phase of treatment, might be more effective.[14]

Treatment with interferon, even for only seven days, was associated with more nasal symptoms, particularly blood tinged mucus, than placebo, but the frequency and severity of these side effects were low and did not increase much with repeated courses. None of the volunteers made detectable circulating interferon binding antibodies.

What do these papers show? Firstly, studies of this sort are feasible—though clearly hard work and expensive. Next, they confirm that interferon can effectively protect against rhinovirus colds in close family contacts—but is this worth while and how should it be implemented? At best, colds are a nuisance lasting a week, though they have considerable

economic importance; at worst, they may precipitate serious exacerbations of chronic bronchitis and other illness, so there are clear indications to prevent colds in susceptible people. Rhinoviruses account for only about 40% of colds, however,[6 10] and clearly it will not be possible to prevent even all of these, since the source of the virus is not always easily recognised. In busy hospitals and general practice, for example, staff are frequently exposed to acute viral infections, and it would be difficult to define what sort of contact would warrant instituting prophylactic treatment. Interferon sprays would have to be cheap and made freely available so that treatment could be started soon enough to be effective—and in view of the effects on the nasal mucosa, long term treatment may need to be discouraged.

Recent evidence suggests that cold viruses are more likely to be transmitted by direct hand to mucosa contact than by inhaled aerosol droplets.[6 15] For the future, interferon holds great promise, but for the present perhaps more emphasis should be put on attempts to reduce transmission of infection by simple hygienic measures—such as diligent handwashing after every contact.

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Steroids, the eye, and general practitioners

Since their introduction in the early 1950s topical steroids have transformed the management of inflammatory disease of the anterior segment of the eye. Their proper use may be sight saving; their inappropriate use is potentially blinding. While they produce a rapid relief of symptoms, at the same time steroids may mask adverse effects. Patients may exert considerable pressure for their prescription and may misuse them once supplied. More than 30 years have passed since Thygeson *et al* first pointed out the potential hazards[1]; these have been confirmed and documented many times, and warnings now appear in textbooks, the *British National Formulary*, and *MIMS*.

Herpes simplex of the cornea is a major ophthalmic problem. A simple dendritic epithelial lesion may be converted by treatment with steroids into an extensive "amoeboid" ulcer affecting all the layers of the cornea and requiring prolonged and complicated management with the likelihood of permanent corneal scarring and loss of vision. These dangers were described in detail at a symposium on herpes simplex eye disease by Williams *et al*[2] and Jones *et al*,[3] who showed how patients given steroids had lesions that were more severe and had increased rates of recurrence and morbidity. They argued that "no undiagnosed red eye should ever be treated with steroids before referral to an ophthalmologist" and called for active communication between ophthalmologists and general practitioners to prevent this misuse.

Bacterial and fungal invasion may also be potentiated by the use of topical steroids. A simple corneal abrasion may become infected. Such infections, particularly with organisms of the pseudomonas group, may progress to a panophthalmitis within hours. The increasingly widespread use of soft contact lenses is an added source of problems. Such lenses are often difficult to maintain and may themselves be a source of infection.

Prolonged medication with topical steroids may lead to open angle glaucoma. Some patients ("steroid reactors") are particularly prone to such a rise in intraocular pressure. Though short term ocular hypertension may not be of great visual significance, prolonged hypertension may lead to cupped disc, field defects, and permanent loss of vision.

Cataracts have been reported after the prolonged systemic use of steroids and also after topical application. Such cataracts may be treated surgically and are not, therefore, quite so disastrous for the patient as infection and glaucoma; none the less, they are better avoided.

Against that background doctors should be disturbed that a questionnaire circulated widely in Britain in 1984 by Claoue and Stevenson found that many ophthalmologists had seen recent examples of the misuse of topical steroids causing serious visual defects (p 1450). The data are to an extent anecdotal but provide a convincing indication of trends. In a second study Lavin and Rose analysed the previous treatment of patients attending an eye accident and emergency department and found further grounds for concern (p 1448). They point out the difficulties that general practitioners have in making a correct diagnosis. This difficulty in diagnosis may lead to the inappropriate use of topical steroids, but steroids were also sometimes prescribed inappropriately when the diagnosis was correct and other more simple remedies were available.

Topical steroids are used by ophthalmologists in herpes simplex keratitis, but always covered by an appropriate antiviral drug. Their use requires considerable experience and careful microscopic control to titrate the treatment against the clinical condition. This can be carried out only in an ophthalmic department and should never be initiated elsewhere.

Communication between the individual ophthalmologist and the general practitioner is paramount, and not merely to underline the textbook warnings of adverse effects. The current papers reiterate the difficulties. Not only should the plea of Jones *et al* be totally reaffirmed—that topical steroids should never be given for an undiagnosed red eye—but many consultant ophthalmic surgeons believe that no treatment with such drugs should ever be initiated by a general