Antiviral Research, 4 (1984) 71–74
Elsevier

AVR 00118

Pharmacokinetics of intranasally applied medication during a cold

R.J. Phillpotts*, Helen W. Davies, J. Willman, D.A.J. Tyrrell and P.G. Higgins

Common Cold Unit, Coombe Road, Salisbury, Wiltshire, England

(Received 12 August 1983; accepted 7 October 1983)

The rate at which interferon is cleared from the nose after local administration was measured in volunteers both before and after challenge with virulent strains of human rhinovirus. Interferon was not cleared more rapidly after virus challenge, and there was no relationship between the amount of nasal secretion produced after challenge, and the rate of interferon clearance. These findings suggest that an inverse relationship between the quantity of a locally applied antirhinovirus drug which is recovered in nasal wash, and clinical and laboratory evidence of rhinovirus infection may be taken as evidence for a beneficial effect of the drug.

interferon; pharmacokinetics; rhinovirus infection

Human interferon α (HuIFN-α) given by means of an intranasal spray, is extremely effective in preventing rhinovirus colds [6,7]. An examination of the therapeutic effects of interferon on established rhinovirus infection is of considerable interest. However, therapeutic treatment of rhinovirus colds might not be successful if interferon was rapidly 'washed out' of the nose during rhinorrhoea. Some preliminary experiments suggested that wash out of intranasal medication during a cold did not occur, and in order to confirm and extend these findings we have measured the rate at which HuIFN-α_2 is cleared from the nose both before and after challenge with virulent strains of human rhinovirus.

These experiments were approved by the Ethical Committee of Northwick Park Hospital, Harrow, Middlesex, U.K. Volunteers were screened for suitability, and housed in isolation at the Common Cold Unit according to our usual procedures [2]. Results were accumulated from two 10-day trials. After 3 days of isolation, volunteers were challenged with nasal drops containing approximately 1 000 50% cell-culture

* To whom correspondence should be addressed.

infective doses of human rhinovirus (HRV) 'DAJT' (an untyped 'wild' rhinovirus) or HRV9 followed after 1 h by a similar dose of HRV14. Daily records of clinical signs and symptoms of coryza, and the weight of nasal secretion produced were kept as previously described [2]. Intranasal clearance of interferon was examined on the day before, and on either day 3 (if symptoms of a cold were present) or on day 4 after virus challenge (with or without cold symptoms). HuIFN-α_2 (Schering-Plough, purified to $> 10^8$ IU/mg protein specific activity was self-administered by volunteers using the manually activated Schering-Plough intranasal spray. Each nostril received approximately 10^5 U 3 times during the day at 3-h intervals. This dose has no therapeutic effect upon established experimental rhinovirus infections (data not shown). Nasal washings were taken either 5, 20 or 60 min after a dose of interferon, so that one wash at each time interval was obtained from every volunteer. Volunteers were randomly allocated to all possible permutations of the 5-, 20- and 60-min time interval series to compensate for diurnal changes in the mucociliary clearance rate. The amount of interferon present in each nasal wash was estimated by immunoradiometric assay [8]. The MRC international reference standard for human leucocyte interferon 69/19 was used to standardise the assay, and interferon concentrations are expressed in IU/ml.

Twenty-eight volunteers were challenged with rhinovirus, of whom 9 developed

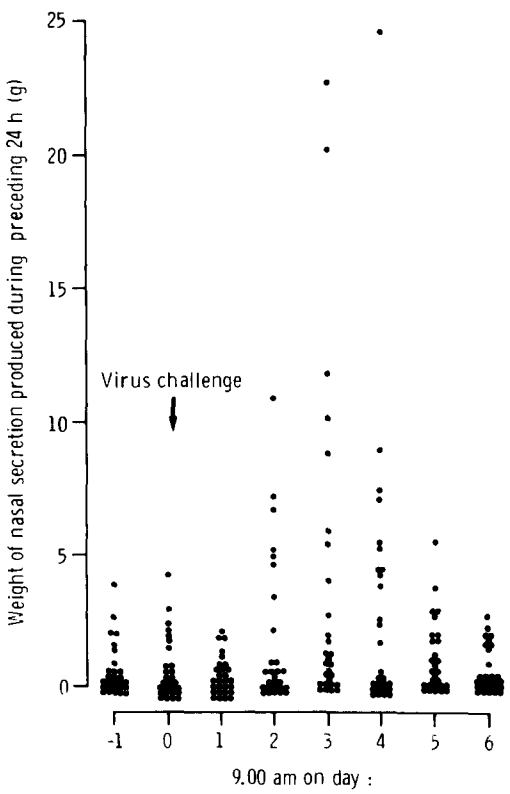

Fig. 1. Daily nasal secretion from 28 volunteers challenged with rhinoviruses.

definite colds (classified as mild, moderate or severe, total clinical score > 14); 11 volunteers (including all those with definite colds) had significant rhinorrhoea (>4 g nasal secretion produced on any one day). The quantity of nasal secretion produced by this group of volunteers is shown in Fig. 1. The concentration of interferon present in nasal wash samples taken at 5, 20 and 60 min after a dose from volunteers both before and after virus challenge is shown in Fig. 2. Although initial interferon concentrations were lower after virus challenge than before, the difference was not statistically significant, and there was no apparent change in the rate of interferon clearance after virus challenge. The initial half-life of intranasally applied interferon both before and after challenge was of the order of 20 min, which is in agreement with our previous findings [3]. There was no significant correlation of the concentration of interferon in 5-, 20- and 60-min nasal wash samples with the amount of nasal secretion produced after virus challenge (the quantity of nasal secretion produced was measured from 24 h before to 24 h after the start of the experiment: $r = 0.054, 0.058$ and 0.043 for 5-, 20- and 60-min samples, respectively, $P > 0.1$ for all values of r). Nor was statistical significance reached when the rate of clearance, expressed as the reciprocal of the difference between the 5- and 20-, 5- and 60- or 20- and 60-min nasal wash interferon concentrations was tested for correlation with nasal secretion weight ($r = 0.171, 0.072, -0.171$, for 5-, 20- and 60-min values, respectively, $P > 0.1$ for all values of r). Analysis of the data from only those volunteers with definite colds yielded similarly negative findings.

These experiments show that the rate at which HuIFN-α_2 is cleared from the nose is not substantially altered during a cold. Therefore, it seems likely that high concentrations of interferon could be maintained in the nose during rhinovirus infection by means of an intranasal spray. As HuIFN-α_2 is cleared from the nose at a rate similar to

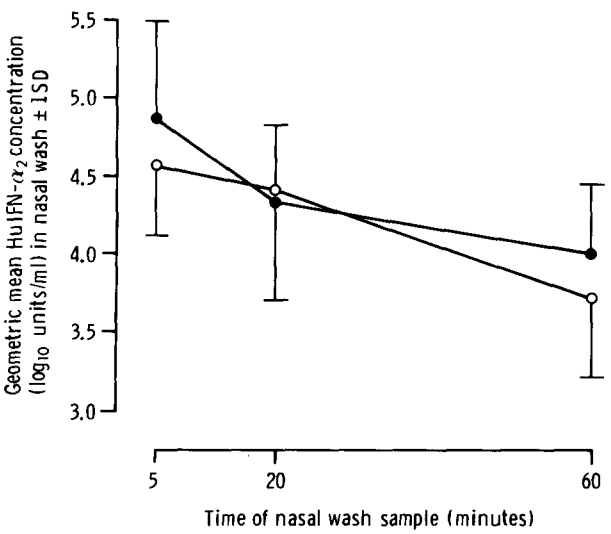

Fig. 2. Rate of HuIFN-α_2 clearance from the nose in volunteers before, ●, and after, ○, rhinovirus challenge. Interferon concentrations in nasal wash were estimated by immunoradiometric assay.

other protein solutions [1] our findings may be generally applicable. Accordingly, a negative correlation between the quantity of an antirhinovirus drug present in the nose and clinical and laboratory evidence of rhinovirus infection would suggest that the compound has a beneficial effect. Such a relationship has recently been found in volunteer challenge studies in which the benzimidazole derivative, enviroxime, was used [4,5]. Further study of the pharmacokinetics and methods of intranasal drug administration might explain why low drug levels are found in certain individuals, since this problem needs to be solved before a local treatment of the common cold is likely to succeed.

Acknowledgements

The technical assistance of Nicky Bailey, Caroline Dearden and Linda Treagust is gratefully acknowledged. This work was financially supported by the Medical Research Council of Great Britain. The HuIFN-α_2 was a gift from the Schering-Plough Corporation.

References

1 Aoki, F.Y. and Crawley, J.C.W. (1976) Distribution and removal of human serum albumin-technetium 99M instilled intranasally by drops and spray. B.J. Clin. Pharmacol. 3, 869–878.

2 Beare, A.S. and Reed, S.E. (1977) The study of antiviral compounds in volunteers. In: Chemoprophylaxis and Viral Infections of the Respiratory Tract, Ed. Oxford, J. (CRC Press, Cleveland, Ohio) pp. 27–55.

3 Davies, H.W., Scott, G.M., Robinson, J.A., Higgins, P.G. and Tyrrell, D.A.J. (1984) The comparative intranasal pharmacokinetics of rDNA human α_2 interferon using two spray systems J. Interferon Res., in press.

4 Phillpotts, R.J., Jones, R.W., DeLong, D.C., Reed, S.E., Wallace, J. and Tyrrell, D.A.J. (1981) The activity of enviroxime against rhinovirus infection in man. Lancet ii, 1342–1344.

5 Phillpotts, R.J., Wallace, J., Tyrrell, D.A.J. and Tagart, V.B. (1983) A study of the therapeutic activity of enviroxime against rhinovirus infection in volunteers. Antimicrob. Agents Chemother. 23, 671–675.

6 Scott, G.M., Phillpotts, R.J., Wallace, J., Secher, D.S., Cantell, K. and Tyrrell, D.A.J. (1982) Purified interferon as protection against rhinovirus infection. Br. Med. J. 284, 1822–1825.

7 Scott, G.M., Phillpotts, R.J., Wallace, J., Gauci, C.L., Tyrrell, D.A.J. and Greiner, J. (1982) Prevention of rhinovirus colds by human interferon alpha-2 from *Escherichia coli*. Lancet ii, 186–188.

8 Walker, J.R., Nagington, J., Scott, G.M. and Secher, D.S. (1982) An immunoradiometric assay of serum interferon using a monoclonal antibody. J. Gen. Virol. 62, 181–185.