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REVIEW

Oral Use of Interferon

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ABSTRACT

Interferon-α (IFN-α) given orally has biological activity in humans and other animals. The dose providing the most benefit delivers IFN-α to the oral mucosa in a concentration (10^2–10^3 IU), similar to that naturally produced in the nasal secretions during respiratory infections. In contrast, conventional IFN therapy employs parenteral doses of $>10^6$ IU and, for this reason, orally administered IFN therapies have been called low-dose treatments. Efficacy in both animal disease models and human studies has been reported, and the mechanisms whereby oral administration has a systemic effect are under active study in a number of laboratories.

INTRODUCTION

THIS BRIEF REVIEW summarizes information from many publications pertaining to oral administrations of interferon (IFN). Because these publications (see references) span a 27-year period, some predate the international standardization of IFN titers in International Units (IU) whereas others used internal laboratory standards. Therefore, it is not always possible to compare studies directly with each other. Nevertheless, the original articles can be reviewed for more detailed information.

In 1972, Tom Schafer *et al.*,[1] then working for Schering Corporation Virology Department, reported that IFN was identified in the milk of mice injected with an IFN inducer and that significantly more newborns survived a fatal virus challenge when IFN was induced in lactating mothers. Thus, the Schering Corporation was the first to report that low doses of orally administered IFN are biologically active *in vivo*.

The earliest record of administration of IFN orally to a human was 20 years ago when bovine IFN recovered from nasal secretions (NS) was offered to a woman as an oral treatment for melanoma.[2] The woman took bovine NS IFN orally three times per day every other week over 2 months, and experienced remission of all tumors. Today, she is still living and remains free of melanoma. The rationale for this therapy was based on the literature at the time which indicated that bovine IFN was active on human or primate cells,[3–7] and the earlier article by Schafer *et al.*[1] documenting appearance and antiviral effects of IFN in milk.

From these anecdotal and modest beginnings, interest in the oral use of IFN was born. Several animal experiments on the efficacy of low-dose oral use of IFN had been performed[8–11] when Diez *et al.*[12] noted that ^{125}I-labeled IFN given intravenously (i.v.) could be found "transiently but in significant amounts in areas corresponding to mouth, nose and paranasal sinuses. . . ." The ^{125}I-labeled IFN-α was likely delivered to these sites in the saliva, possibly through iodide uptake and secretion by salivary glands.[12,13]

IFN given orally is rarely detected in the blood. Schafer *et al.*[1] reported that mouse and rabbit IFNs, when given orally to neonatal mice, were detected in sera. Other workers have given IFN orally to older rabbits,[14] dogs,[15] and monkeys[16] and did not detect serum IFN. IFN-β_{ser} was given orally to 6 human volunteers and neither IFN-β_{ser} nor markers of IFN activity could be detected in sera or leukocytes; however, one subject complained of mild nausea and another reported mild pharyngitis. [17]

BACKGROUND

What are the concentrations of IFN naturally occurring in the nasal and oral cavity? IFN has been identified in pharyngeal washings,[18] saliva,[19] or nasal washings[20–29] of humans, in the nasal washings[30] and nasal secretions[31–35] of cattle, and in the nasal washings of cats.[36] An IFN titer of 2,048 units/ml was reported in the nasal washing of a human subject

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infected with influenza A_2[22] IFN titers ranging from 128 to 1,024 units/ml were reported in 5 human infants infected with influenza A virus.[27] IFN titers ranging from 20 to 640 units/ml were found in 86% of nasopharyngeal aspirates from rhinovirus-positive children.[23] However, most studies reported nasal IFN titers of <100 units/ml, even though different assays, cell cultures, and challenge viruses were employed.[20–29] Nasal administration of an IFN inducer, *N,N*-dioctadecyl- *N′,N′*-bis(2-hydroxyethyl) propanediamine, resulted in detectable IFN (10–250 units/ml) in the nasal washings of 10 of 15 human subjects.[24] The mean nasal secretion titer in cats was reported as $1:12 \pm 1:10$.[36] The nasal secretion titers in cattle were generally $<1{,}000$,[30–34] but a titer of 160,000 was reported.[35] Studies in cattle examined the kinetics of IFN production in the NS.[37–39] Calves inoculated intranasally (i.n.) with various viruses were tested for NS IFN at 1, 2, 4, 6, 7, 8, 10, 12, and 14 days after inoculation. IFN was not detected in the NS before challenge of seronegative calves with infectious bovine rhinotracheitis (IBR) virus, but was detected (titers $\leq 5{,}000$ units/ml) in all 18 calves within 1–4 days after challenge.[37–39] IFN was not detected in the NS of three calves given bovine rhinovirus, [37] and in only one of four calves given bovine adenovirus (BAV)[38]; however, these calves had serum antibody to rhinovirus or BAV at the time of challenge.[37,38] Low levels (<90 units/ml) of IFN were recovered from the NS of three seronegative calves given parainfluenza type 3 (PI-3) virus, but in only one of three calves (16 units/ml) seropositive to PI-3 virus at challenge.[39] The highest NS IFN level (10,000 units/ml) detected in 34 calves given a combination of viruses was noted in a calf given IBR virus followed 4 days later by BAV.[37–39] This relatively high IFN titer may be an example of *in vivo* priming. When IBR virus was given i.v. to calves, only low IFN titers (<23 units/ml) were detected in serum,[40,41] suggesting that the nasal route of IBR virus (respiratory tract) was superior as a method for inducing IFN.

IFN was detected (maximum titer of 600 units/ml) in the turbinates, but not in the nasal washings or blood of ferrets inoculated with influenza virus.[42] IFN was applied i.n. by Pasteur pipette to the mucosal surface of the inferior turbinates of adult chimpanzees and humans and then the area of application was scraped at 0 and 5, 10, 15, 30, and 60 min thereafter. Recovery of titratable IFN was reduced 5- to 500-fold within 60 min, indicating that nasal mucociliary clearance mechanisms transported the IFN to the posterior pharynx.[43]

Can low concentrations of IFN affect cells in the oral cavity? In a mucosal epithelial cell line, IFN-α enhanced interleukin-1α (IL-1α), augmented neutrophil-mediated anticandidal action,[44] and increased HLA-DR expression by human buccal epithelial cells.[45] *In vitro*, low concentrations (10–10,000 IU/ml) of IFN-α increased the secretion of IL-8 in human immunodeficiency virus type 1 (HIV-1)-infected U937 (myelomonocytic) cells,[46] and enhanced expression of intracellular adhesion molecules-1 (ICAM-1), integrin-α2 and integrin-β1.[47]

In vivo, the oral use of low doses of IFN-α, -β, or -γ exhibited systemic effects in mice,[48–66] cats,[67] dogs,[68] cattle,[69–71] horses,[72] swine,[73,74] rats,[75–78] and guinea pigs.[79] Some reports claim low-dose orally administered IFN-α is beneficial in humans with AIDS,[80–83] multiple sclerosis,[84] Sjögren's syndrome,[85] hepatitis B,[86,87] neuromuscular disease,[88,89] aphthous stomatitis,[90,91] oral mucositis associated with cancer chemotherapy,[92] and measles.[93] Other reports claim no benefit in AIDS[94–96] or cancer.[97] Although much higher doses (4.5×10^8 IU, then 1.35×10^9 IU) of oral IFN-β had no measurable effect in humans,[17] high doses (10^5 IU) of IFN-α used orally were reported to be beneficial in viral disease and cancer in mice.[98–100]

CONCLUSIONS

One of the paradoxes of the efficiency in the oral use of IFN is the dose effect. Here, "less" is almost always better than "more." In most of the low-dose studies of IFN-α, used orally, where a beneficial dose was identified, increasing the dose did not improve the effect. For example, 50 IU of human IFN-α given orally was more beneficial than 450 IU in treatment of horses with inflammatory airway disease.[72] An extremely low dose (<1 unit) is reported beneficial in guinea pigs[79] or mice.[56] In our opinion, it appears that IFN doses that approximate the concentration of IFN that can be induced in the NS result in the most clinical benefit. The observed benefit can only be explained rationally by priming effects of the administered IFN for various facets of host defenses. The stage has been reached where the effects of low doses of IFN used orally have been documented in various experimental and clinical situations. What is not yet determined are the details of the mechanism(s) of action from the time of oral administration to the final effect of the therapy.

From its modest beginnings 20 years ago, the interest in the uses of the oral route for IFN and other biologically active signaling molecules has grown dramatically.[101–103] The currently accepted method of IFN administration by injection of millions of IU is obviously not physiologic; it does not duplicate the levels of this potent biological regulatory factor as found in vivo. Indeed, the notion that low doses of oral administered IFN-α may mimic natural defense processes occurring during respiratory infections has theoretical appeal.

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