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Antiviral Research 24 (1994) 111–119

Antiviral Research

Pharmacology and side-effects of interferons

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(Received 4 November 1993; accepted 14 February 1994)

Abstract

The distribution, catabolic sites and turnover of interferons are reviewed in order firstly to improve their utilization, secondly to reduce toxicity and thirdly to evaluate alternative routes of administration. In fact catabolic pathways are now seen as a salutary system capable in most cases to reduce toxicity to an acceptable level.

Key words: Interferon; Catabolic pathway; Side-effects; interferon

1. Introduction

Interferons (IFNs) are proteins (most of the α subtypes) and glycoproteins (IFNs ω, β and γ) which, while they present some amino acid homology, show significant physicochemical differences such as hydrophobicity (IFN $\beta > \gamma \geqslant \alpha$) and carbohydrate content. These differences are partially responsible for their different distribution, catabolism and to some extent therapeutic efficacy (Bocci, 1983, 1987). IFNs exert pleiotropic activities, but in practice they can be used either as antiviral or antiproliferative drugs and/or as immunomodulators. Thus, depending upon the main therapeutic scope, we can apply pharmacological concepts similar to those used for cytotoxic drugs, while for use in immunomodulation we have to bear in mind that IFNs induce prolonged biological and immunological effects which last far longer that their actual half-life. On this basis our mentality, accustomed to the use of antibiotics, must change and new dosages, schedules and routes of administration must be sought to achieve a good therapeutic index (Bocci, 1985a). This

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SSDI 0166-3542(94)00008-V

seems now feasible because there are more effective pharmaceutical formulations that may allow, at least in part, IFN absorption through epithelial barriers. In order to use IFNs at their best, it is necessary to know their pharmacokinetics, biologic activities and mechanisms of action that will be briefly discussed herein.

2. Metabolism and turnover of IFNs

These depend upon the IFN type and the route of administration. However when they are administered via the intravenous (IV) route and mix in the plasma, several processes, such as transendothelial passage, cell binding and catabolism, occur simultaneously; some IFN passes from the plasma pool into the interstitial fluids of various organs, some is either taken up by the liver or filtered by the kidneys, and some becomes bound to circulating leukocytes and to endothelial and parenchymal cells (Bocci, 1987). Transcapillary passage of IFN molecules is regulated by blood pressure, flow and capillary permeability and is almost total in the liver, spleen and bone marrow, partially reduced in the kidneys, intestines and skin, and, with an exception, almost negligible for muscles, lungs, subcutis, bone tissue and the central nervous system (CNS). Capillary permeability of solid tumors may be quite variable. As a consequence the amount of IFN actually reaching tumor cells is not predictable, nor is the small amount reaching the neoplastic environment necessarily active, as proteinases, antagonists and inhibitors may quench its activity (Bocci et al., 1990). Thus the failure of IFN to influence growth of solid tumors is not surprising, particularly in neoplasms secluded in anatomical sanctuaries.

Movement of IFN from plasma into several pools occurs at different rates and implies a complex and multiexponential decay (Bocci et al., 1985a). However, in practice, the disappearance of IFN from plasma is described and analyzed as a biphasic curve; it has been assessed using a two-compartment, open model described by the equation $C_t = Ae^{-\alpha t} + Be^{-\beta t}$ where C_t is the concentration of IFN, A and B are concentration values after extrapolation at the time of injection, and α and β are constants estimated by using standard methods. Serum half-lives ($t1/2$) of IFN during the initial (fast) distribution phase and the successive (slow) elimination phase are calculated as $0.693/\alpha$ and $0.693/\beta$, respectively. It is useful to note that half-life values of IFNs, when used as a biological response modifier (BRM), should be taken only as an indication that they remain briefly in the circulation, while in fact biologic effects last longer so that it is not necessary to maintain IFN at a steady level. Actually this may be more detrimental than useful because target cells may be depleted of receptors or be in a refractory state so that IFN acts prevalently on normal cells, thus increasing toxic effects. As extensively reviewed before (Bocci, 1987), there is a considerable variability in half-life values; this is largely due to various dosages, and usually a high dosage yields a half-life longer than a small one. Moreover, repetitive daily doses tend to have a similar effect, which suggests that saturation and down-regulation of cell receptors have some role in this phenomenon (Billard et al., 1986; Lau et al., 1986).

After IV administration as a bolus, the half-lives (slow phase) of leukocyte IFN

and human rIFN α_2 are of about 1.5 and of 0.75–2 h, respectively (Bornemann et al., 1985). Metabolic heterogeneity of IFN is evident by observing that after IV administration half-lives (slow phase) of natural IFNs β and γ are of only β and of 2.6–31 min, respectively (Gutterman et al., 1984). Human R IFN β (serine) and R IFN γ (*E. coli*) display similarly half-lives of 70 (Hawkins et al., 1985) and of 30 min (Gutterman et al., 1982), respectively.

IFNα administered via the intramuscular (IM) and the subcutaneous (SC) routes are absorbed from injection site and reach the plasma pool so that IFN plasma levels increase progressively during the first 5 to 9 h (t_{max}) and then slowly decline because the amount of IFN that disappears from the plasma is greater than that either being absorbed or returning via the lymphatic or blood vessels. The IFN peak level (C_{max}) is obviously much lower than that achieved immediately after IV administration, but IFN plasma levels are sustained for longer and become undetectable 16–24 h thereafter. Either IM or SC administration of IFN yields similar plasma curves, although the IFN peak level may be slightly delayed after SC injection. After IM administration of leukocyte IFN and R IFN α_2, half-lives of about 7 (Gutterman et al., 1982) and of 5–8.2 h, respectively, have been measured (Bornemann et al., 1985). On the other hand, both natural IFNs β and γ are hardly detectable in the plasma after IM administration (Treuner et al., 1981; Gutterman et al., 1984), and it seems more proficient to administer these IFNs by slow IV infusion. However, R IFN β serine and R IFN γ (unglycosylated), after IM administration, yield a plasma curve with half-lives of 70 and of 227–462 min, respectively, although some of the circulating R IFN γ, measured by immunoassay, is biologically inactive (Kurzrock et al., 1985).

The conclusion that natural human IFN β is inactive after IM administration, because it remains fixed or is catabolized at the injection site is partly incorrect, because, by simultaneously sampling plasma and lymph from the rabbit cisterna chyli, we have shown that IFN β is absorbed also via lymphatics (Bocci et al., 1988). This result explains why IFN β, in spite of undetectability in plasma, causes increased (2′–5′) oligoadenylate synthetase and β_2 microglobulin levels, enhanced natural killer activity, and increased expression of hormonal receptors (Lucero et al., 1982). During its transit through the lymph and lymph nodes, IFN β comes into contact with a great number of effector cells and, as it slowly emerges into the plasma, undergoes considerable dilution and rapid breakdown so that its level remains negligible. This explains why IFN β after IM administration is somewhat better tolerated than an equivalent dose of IFN α, the bioavailability of which is almost quantitative. Indeed there is a good correlation between toxicity and IFN plasma levels and moreover constant plasma levels yield worse toxicity than intermittent ones.

3. Side-effects of IFNs and their possible pathogenesis

The concept that IFNs, being a natural product, would not be toxic was a naive one because in fact undesirable side-effects have been reported after administration

Table 1
Deleterious effects of interferons in the following:

Fetus	Newborns (mice and rats)
Abnormalities in mice	Inhibition of growth
Apparent normal growth in humans	Massive liver necrosis with 100% lethality ($1\ LD_{50} \leqslant 88$ ng IFN/day/mouse)
	Glomerulonephritis

Adult humans ($1.5–10 \times 10^6$/day or more)				
Nausea	Malaise	Chills	Bone marrow depression	Confusion
Anorexia	Fatigue	Shivering	Elevation of transaminases	Conceptual disorganization
Vomiting	Low-back & joint pain	Fever	Fall of HDL	Psychomotor slowing
Diarrhoea	Neck stiffness	Skin	Hair loss and skin reactions	Speech stoppage
Weight loss	Myalgia			Thought blocking
	Headache			Paresthesia
				Coma

of pure IFNs. It is therefore well understandable why the appearance of IFN during an acute viral infection is transient: on the one hand there is a shutoff of IFN synthesis and, on the other, the efficiency of the catabolic system ensures a rapid clearance of IFN. In spite of its rapid disappearance, the IFN response is frequently sufficient to block viral spread and to favour an effective immune response.

Table 1 summarizes most of the known side-effects occurring during prolonged IFN treatment. It must be emphasized that it is not yet known whether IFN has teratogenic effects on the foetus and, as a precautionary measure, it appears preferable to avoid IFN therapy in women during the first 3 or 4 months of pregnancy. However two patients with chronic myelogenous leukemia and two patients with hairy cell leukemia treated with IFNα during pregnancy have recently given birth to apparently normal infants (Baer et al., 1992). Mice seem far more sensitive because IFNγ to pregnant mice leads to developmental abnormalities, pancytopenia and abortion (Vassiliadis and Athanassakis, 1992). As far as newborn mice and rats are concerned, daily inoculation of potent IFN preparations is lethal (Gresser et al., 1975, 1976). A possible explanation is that for about 1 week after birth these rodents have an immature and inefficient catabolic system for eliminating IFN. This situation, which is to some extent similar in human newborns, when associated with huge IFN dosages, probably leads to abnormal IFN retention in plasma. Liver growth is blocked (Jahiel et al., 1971) and actually the arrest of the hepatocyte life cycle seems irreversible because extensive cell death follows. In fact, if IFN administration is discontinued after 6 to 8 days, the animals do not die of liver necrosis but glomerulonephritis will ensue with death later. The cause of nephritis is also unknown but it can probably be related to the liver degeneration or to a direct deleterious effect of IFN on the glomeruli. Thus, unless we are dealing with life-threatening diseases, the use of IFNs in newborns requires some caution.

Toxicity of IFNs in adults is far less dramatic but nonetheless it has to be taken

into account because sometimes it leads to such discomfort that the patient is forced to discontinue the therapy. After a single injection of about 3×10^6 units of IFNα, acute toxicity is mainly characterized by fever often preceded by shivering. The increase of body temperature (at most +2°C) is monophasic, reaches a zenith in about 8 h and returns to normal in the following 10 h (Scott, 1983; Bottomley and Toy, 1985). The causes of the pyrogenicity of IFNs are due to the direct or indirect (either via induction of interleukin 1 od/and activation of prostaglandin-synthetase) effect in the thermoregulatory center in the pre-optic region of the hypothalamus (Bocci, 1980). Although the central nervous system (CNS) is endowed with the blood-brain barrier (BBB) there is a permeable area that is about 5000-fold smaller than that of the whole BBB, which explains the pathogenesis of several toxic effects (Table 1). This area comprises the circumventricular organs (CVO_s), which by being vascularized with capillaries, open junctions and fenestrations (Van Deurs and Koeler, 1979) are permeable to cytokines, viz IFNs, IL-1, IL-2, IL-6 and TNFα (Stitt, 1990). The CVO_s, composed of the hypothalamic median eminence, the organum *vasculosum laminae terminalis*, the choroid plexus, the subfornical organ and the area postrema, include a number of functional centres controlling thermoregulation, sleep, the emetic trigger zone and neurosecretion (Blatteis, 1990; Spath-Schwalbe et al., 1989; Muller et al., 1991). The interaction of cytokines with either endothelial or/and glial and neuronal cells of these centres causes the release of free radicals and prostaglandins as well as an alteration of neurotransmitter functions with the appearance of most of the symptoms elencated in the Table. Some details of mechanisms of action have been reviewed before (Bocci, 1988) and remain valid also on the basis of experimental findings by Farkkila et al. (1988).

On the whole bone-marrow depression and CNS toxicity appear the most important dose-limiting factors and although they are reversible, one has to discontinue the therapy or reduce the dosage. Besides the usual symptomatic treatment with indomethacin or/and paracetamol, tachyphylaxis ensues in the majority of patients. However, aged patients may experience intolerable fatigue and mental confusion suggesting alterations of the cortical neurons and a possible down-regulation of end-plate activity (Renault et al., 1987; Smith et al., 1988). Quite a few patients complain about a diminution of libido.

In patients with pregress cardiovascular disorders it is possible that IFN therapy exacerbates this pathology. Prolonged IFN treatment may also induce or enhance autoimmune diseases as well as autoantibody formation but this problem will be dealt with by Antonelli in this issue of the journal.

While there is little doubt that the problem of IFN toxicity can be serious, particularly with patients who do not understand the evolution of their diseases, it is our duty to reduce it by defining the minimum effective dose and to use the route of administration and schedule more suitable for each particular disease. For chronobiological reasons administration of IFN in the evening is useful because it has either a somnogenic effect or/and it disturbs the cortisol cycle and lymphocyte circulation less (Bocci, 1985,b).

4. Is there an optimal route, dose and schedule for administering IFNs?

It is already clear that each disease susceptible to IFN ought to be treated with an appropriate dose and schedule for achieving the best therapeutic index. Some general principles are suggested as follows: there is no advantage in maintaining high and constant IFN levels in plasma, as can be achieved by continuous IV infusion (theoretically useful in treating acute viral diseases or neoplasma with IFN as a cytotoxic drug), because renal and hepatic catabolism are related to the IFN concentration and therefore there is a huge loss of IFN (Bocci, 1987). It must be borne in mind that unfortunately IFN is not a selective drug, and while it may or may not inhibit tumor growth, it certainly inhibits proliferation of normal cells, particularly in the bone-marrow and intestines. Assuming that the tumor is responsive, antiproliferative effects are IFN dose-dependent, but the achievement of effective concentrations in the neoplastic environment implies high IFN plasma levels that would be either intolerable or deadly. Also for tumor-necrosis factor α (TNFα) and interleukin-2 (IL-2) we have realized that effective concentrations in the plasma cannot be maintained for days as it is in a culture-plate.

As a consequence, whenever possible, regional therapy is desirable because it can yield a better therapeutic index. This has been achieved by different means such as intra- or peritumoral, or intra-arterial administration with or without preliminary capillary embolization with biodegradable materials (Civalleri et al., 1986). Other possibilities already pursued (extensively reviewed elsewhere, Bocci, 1992) are the intraperitoneal or intrapleuric administration; in these cavities, IFN concentrations may be many-fold higher than blood levels allowing a prolonged cytostatic action (at a very short range, i.e., <5 mm) and a slow IFN clearance with a possible immunoadjuvant effect. Absorption of IFN via lymphatics may also be effective in controlling metastases.

In order to overcome viral persistence in the CNS where about 95% of capillaries are tightly closed and impede the transfer of IFN from the plasma into the CNS interstitial fluid, two approaches have been followed: the first is to deliver IFN via carotid or vertebral circulation, while the BBB has been made transiently permeable by either bile salts or hypertonic mannitol (Neuwelt and Rapoport, 1984). The second is to administer IFN into the CNS more or less directly; the intralumbar route is frequently used but allows a partial perfusion of CNS, while the intraventricular route, via Ommaya's reservoir, favors a wider distribution of the drug. Among conventional routes, SC administration of IFN appears the most practical one for the prolonged treatment of hematological neoplasia and chronic viral infections. This is probably due to the fact that IFNα is almost completely absorbed from the site of injection both via venous and lymphatic capillaries and IFN acts either as an antiviral or/and an immunomodulator drug. Particularly when we are treating chronic hepatitis we should aim on one hand to activate antiviral mechanism in the hepatocyte and on the other, to stimulate cytotoxic cells for killing selectively virus-infected or transformed cells. Unfortunately IFN does not have a selective affinity for hepatocytes and some toxicity appears unavoidable unless we devise a novel delivery system.

In recent years there has been considerable interest in trying to inhibit the intestinal proteolysis and to overcome the enterocyte barrier hoping to allow absorption of insulin and IFNs. Both the intestinal and rectal routes are being evaluated but only the latter one has yielded encouraging results (Bocci et al., 1985b; Yoshikawa et al., 1986). Due to simultaneous portal and lymphatic absorption of IFN, they would allow a favorable IFN concentration in the liver, as well as enhanced immunoadjuvant effects predictably useful in the treatment of hepatitis and liver tumors.

Another unusual route is represented by the bronchiol-alveolar tree for treating pulmonary viral diseases with IFN aerosol. This approach may be advantageous because IFN acts locally on an enormous surface, activates bronchoalveolar cells, enhances the immune response (Debs et al., 1988) and produces only mild side effects, because it is inactivated during transalveolar passage as shown directly in isolated lungs (Bocci et al., 1984) and indirectly in vivo (Maasilta et al., 1991).

5. Conclusions

It has taken several years of clinical trials to select the appropriate IFN type, dosages, routes and schedules of administration. Both recombinant and 'natural' IFNs α are the most used by SC route for prolonged treatment of chronic viral diseases, particularly hepatitis, and a few responsive malignancies. Excessive dosages, poor metabolic conditions and ageing often lead to untolerable toxicity and to poor patient's compliance. Thus, in order to improve the therapeutic index we must use our best discernment in perfecting dosage schedules and more rational routes of administration. Novel approaches of IFN delivery via the nasal-oro-pharyngeal, intestinal, rectal and broncho-alveolar surfaces and lymphatic system supported by new pharmaceutical formulations are being pursued hoping to enhance the host immune system with negligible side-effects.

Acknowledgements

I am grateful to my wife Helen for linguistic revision. This work has been supported in part by MURST (40%) and by the National Research Council (CNR, Rome) – Targeted Project "Applicazioni cliniche della ricerca oncologica", ACRO.

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