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Short Communication

Pharmacokinetics of recombinant interferon alpha-C

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Summary. Recombinant interferon alpha-C (rIFNα-C, Interpharm), is a new type of alpha-interferon that has a specific activity of $1-2\times10^9$ units/mg protein. The pharmacokinetics of rIFNα-C were studied in 11 patients with metastatic renal-cell carcinoma. A total of 10 million units IFNα-C were injected intramuscularly and the serum level of IFN was evaluated up to 72 h post-administration. Measurable IFN concentrations appeared in the serum as early as 0.5 h, and levels peaked at 4–6 h ($C_{max} = 53.2 \pm 4.6$ units/ml). Relatively high levels persisted for 24 h and declined thereafter with an apparent half-life of 3–4 h. The mean area under the serum-concentration curve (AUC) was $1{,}259 \pm 145$ units h ml^{-1}, indicating good bioavailability of the preparation from the intramuscular injection.

Introduction

Although the pharmacokinetics of interferon (IFN) α-C are unknown, those of other IFN species, including the closely related IFNα-A, have been studied extensively and reviewed [1, 2, 8, 11]. Available data on the pharmacokinetics of IFNα-A preparations indicate good bioavailability characteristics following intramuscular or subcutaneous injection. With such preparations, peak serum concentrations are usually achieved some 3–12 h after intramuscular injection. The major route of elimination of IFN-α seems to be renal tubular metabolism, following glomerular filtration and tubular reabsorption. Serum half-life estimates of 2 8 h have been reported. Usually, serum levels of IFN-α become undetectable at 24 h.

Interestingly, the pharmacokinetic behaviour of IFNα-A in patients with advanced malignancy or in those with renal insufficiency was similar to that in healthy subjects. The present report describes the serum levels and pharmacokinetics of IFNα-C (Interpharm) following intramuscular injection in 11 patients with metastatic renal-cell carcinoma.

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Organization

The pharmacokinetic study of IFNα-C was carried out at the Oncology Department of Ichilov Hospital, Tel-Aviv Medical Center (principal investigator, Dr. Ofer Merimsky). Plasma samples were analyzed for IFN at Interpharm Laboratories, Ness Ziona (Dr. Dina Fischer). The study was conducted over a 1-year period from July 1988 to July 1989.

Materials and methods

Interferon. Recombinant IFNα-C (rIFNα-C; Interpharm, Israel) is a new species in the alpha-interferon family. It is characterized by a titer of antiviral units per milligram protein that is 3–5 times higher than that of IFNα-A. Its specific activity is $1-2\times10^9$ units/mg protein, the highest among the IFN-α species presently available; therefore, less protein need be injected to attain the same biological effect. rIFNα-C is highly purified bacteria-derived, and the final product is free of nucleic acids, endotoxin or other bacterial contaminants.

Patient selection. In all, 11 patients with metastatic renal-cell carcinoma (RCC) who were deemed to be suitable candidates for IFNα-C therapy were included in the study. All had stage 4 disease, and some had failed therapy with other treatment modalities. Following completion of the pharmacokinetic study, daily treatment with IFN was instituted on an outpatient basis. Each patient was interviewed and informed of the nature of the study and each freely consented to participate. It was made clear that any patient could withdraw from the study at any time in favor of other medical treatment.

All patients were hospitalized for the pharmacokinetic study. They underwent a thorough medical examination and screening laboratory evaluation. The group consisted of ten men and one woman. The median age was 65 (range, 51–75) years; the median weight, 77 (68–92) kg; and the median height, 169 (157–185) cm. Four of the patients smoked and eight had undergone nephrectomy. The patients were heterogeneous in terms of their general medical state and most received one or more additional drugs for their ailments. Most had normal kidney- and liver-

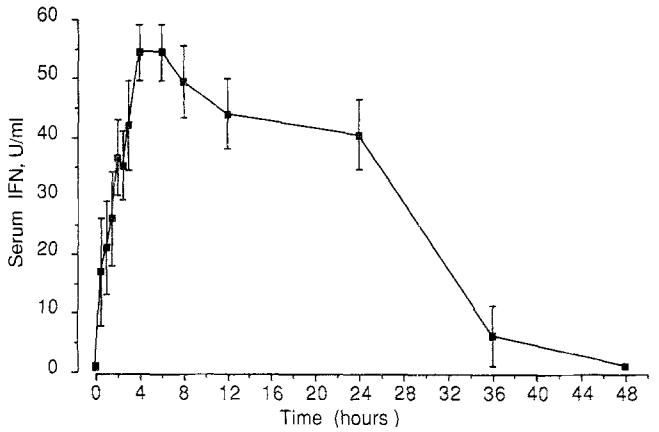

Fig. 1. Mean (±SEM) serum concentration-time curve of recombinant interferon alpha-C

function tests, although four had elevated serum creatinine and/or blood urea nitrogen (BUN) levels and few had showed marginal abnormalities in their liver-function tests. Patients were fed regularly and remained recumbent throughout the study.

Treatment plan. Each patient was adapted with a Venflon intravenous cannula in the antecubital vein. The cannula was kept patient by the injection of 2 ml saline-heparin solution (30 units heparin/ml). rIFNα-C (10 million units) diluted to a volume of 5–10 ml was injected into the gluteus muscle at time 0. Venous blood samples were drawn from the Venflon cannula (the first 5 ml was discarded, then 10 ml blood was collected each time) at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 h. In four cases (patients 1, 4, 9 and 10) sampling was continued at 36, 48, 60 and 72 h. Toxicity was reported according to WHO criteria [10].

Sample handling. Blood samples were collected in glass test tubes and kept at 4° C. They were then centrifuged for 10 min at 2,500 rpm and the serum was transferred into plastic tubes. The sera were delivered to Interpharm in an ice box by courier and were frozen at –20° C until assayed.

Analytical methodology. IFNα-C activity was measured in the serum using the cytopathic effect (CPE) reduction assay, as described in detail in a review by Meager [9]. In this type of assay, cells in microtiter plates are protected with serial IFN dilutions, then challenged with a cytopathic virus and incubated until maximal cell killing in untreated cells (virus control) is obtained. The endpoint for each IFN sample (the well in which 50% of the cells are viable) is determined by dye uptake, which is proportional to the number of uninfected cells. The final IFN concentration is calculated from the ratio between the endpoint dilution of the sample and that of an NIH international standard.

WISH cells with vesicular stomatitis virus (VSV) were used for this CPE inhibition assay. Because high concentrations exhibit and antiviral-like activity in this assay, the presence of IFN activity was demonstrated by comparing the activity obtained in the presence or absence of anti-IFN-α antibodies. The level of IFN activity could be determined only in samples containing higher activity than the serum background level as demonstrated by partial neutralization of the activity by the antibodies. In addition, the IFN antiviral activity and the serum antiviral-like activity are not additive (as shown by spiking serum controls with IFN). Therefore, when part of the activity in a given sample is neuralized, the final activity is calculated without subtracting the background activity.

Results

Figure 1 shows the mean (± SEM) serum concentrations of IFNα-C (in units/milliliter) in the 11 patients studied. Détectable IFN concentrations appeared as early as 0.5 h following the intramuscular injection of 10 million units rIFNα-C, and levels peaked at 4–6 h (C_{max} = 53.2 ± 4.6 units/ml). High IFN levels persisted for 24 h and declined thereafter to undetectable levels at 48 h. The mean area under the serum-concentration curve (AUC), calculated by the trapezoidal rule, was 1,259 ± 145 units h ml^{-1}. In the present study, the apparent terminal serum half-life of IFNα-C after intramuscular injection was estimated to be 3–4 h (Fig. 1).

Four patients had mildly impaired renal function (serum creatinine level, 1.6–1.9 mg%). There was no significant difference in the pharmacokinetics of rIFNα-C between this group of patients and the other seven subjects. Toxicity caused by the single intramuscular injection of 10 million units included grade II fever and flu-like symptoms in ten patients.

Discussion

rIFNα-C was given by intramuscular injection, the mode of administration recommended in the literature to achieve a higher rate of response of metastatic renal-cell carcinoma to interferon therapy [7].

As shown by the present results, the pharmacokinetic behavior of rIFNα-C is remarkably similar to that of IFNα-A, as reported in the liteature. The data indicate good bioavailability of rIFNα-C from the intramuscular dosing form. Systemic absorption from the intramuscular site starts soon after injection, and serum concentrations peak at 4–6 h and remain elevated for at least 24 h. Serum levels in the present investigation (in units/milliliter) are quite comparable with concentrations reported in the literature for IFNα-A preparations after intramuscular injection [4, 12]. In our comparisons, data on IFNα-A that have been reported by others in picograms per milliliter were converted to units per milliliter because of the higher specific activity of IFNα-C. Although the exact bioavailability of the IFNα-C under study cannot be calculated, we can venture an estimate based on available data on IFNα-A [4, 12]. Because serum concentrations and half-lives of IFNα-C are comparable with those of IFNα-A, and assuming that both IFNs probably have similar volumes of distribution, one may estimate that the bioavailability of the present IFNα-C preparation is comparable with that previously reported for IFNα-A, namely, on the order of 80%. The half-life estimate of 3–4 h for IFNα-C is also compatible with similar estimates for IFNα-A [4, 12].

The data in the present study are derived from cancer patients, some of whose liver- and kidney-function test results were outside the normal range. However, it has been shown that neither advanced cancer [4, 5] nor chronic renal failure [6] have any influence on the pharmacokinetic behavior of IFN-α. The same observation was made in our study. The pharmacokinetics of rIFNα-C in patients with mildly impaired renal function showed no significant difference from those in patients with preserved kidney function. It is also reported in the literature that catabolism of IFN-α in contrast to IFN-β species is unrelated to liver function [3].

References

1. Billiau A (1981) Interferon therapy: pharmacokinetic and pharmacological aspects. Arch Virol 67: 121
2. Bocci V (1988) Pharmacokinetics of interferons and practical implications. In: Revel M (ed) Clinical aspects of interferons. Kluwer Academic, Boston, p 259
3. Bocci V, Pacini A, Bandinelli L (1982) The role of liver in the catabolism of human alpha and beta interferon. J Gen Virol 60: 397
4. Bornemann LD, Spiegel HE, Dziewanowska ZE (1985) Intravenous and intramuscular pharmacokinetics of recombinant leukocyte A interferon. Eur J Clin Pharmacol 28: 469
5. Gutterman JU, Fine S, Quesada J (1982) Recombinant leukocyte A interferon: pharmacokinetics, single-dose tolerance and biological effects in cancer patients. Ann Intern Med 96: 549
6. Hirsch MS, Tolkoff-Rubin NE, Kelly AP, Rubin RH (1983) Pharmacokinetics of human and recombinant leukocyte interferon in patients with chronic renal failure who are undergoing hemodialysis. J Infect Dis 148: 335
7. Horoszewicz JS, Murphy GP (1989) An assessment of the current use of human interferons in therapy of urological cancers. J Urol 142: 1173
8. Mannering GJ, Deloria LB (1986) The pharmacology and toxicology of the interferons: an overview. Annu Rev Pharmacol Toxicol 26: 455
9. Meager A (1987) Quantification of interferons by anti-viral assays and their standardization. In: Clemens MJ, Morris AG, Gearing AJH (eds) Lymphokines and interferons: a practical approach. IRL Press, Oxford, p 129
10. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer patients. Cancer 47: 207
11. Scott GM (1982) Interferon: pharmacokinetics and toxicity. Phil Trans R Soc Lond B 299: 91
12. Wills RJ, Dennis S, Spiegel HE (1984) Interferon kinetics and adverse reactions after inravenous, intramuscular and subcutaneous injection. Clin Pharmacol Ther 35: 722