The Kinetics of Human Interferon Clearance in Gibbons (37151)

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An increasing interest in the therapeutic applications of exogenous human interferon suggests that more data are needed on its clearance from the blood following injection; the clinical investigator must have a reasonable basis for selecting dose level, route, and regimen for its administration. It is evident that mouse (1–5) and rabbit (6) interferons are rapidly cleared from the blood of homologous species after intravenous injection. Also, little mouse interferon appears in the blood of mice following intramuscular injection (4). However, it has been unclear whether a human interferon would behave similarly due to the diverse physicochemical properties of interferons (7). Consequently, the clearance of human leukocyte interferon was investigated by Cantell and Pyhälä in rabbits (8). Intravenous injection of the interferon led to a rapid continuous fall in its blood concentration. In contrast, when the interferon was injected intramuscularly or subcutaneously, a lesser fraction of the administered dose was detected in the blood, and the blood levels were sustained for at least 24 hr. It was considered pertinent to examine the clearance of human interferon in primates, since the metabolism, excretion, and tissue distribution of a substance often differ among species. The gibbon (*Hylobates lar*), an anthropoid ape, was selected for study.

Materials and Methods. The interferon used in these studies was produced in human leukocytes by induction with parainfluenza 1/Sendai and was concentrated by precipitation with potassium isothiocyanate according to previously described methods (8). This material, containing 2×10^6 IU/ml, was similar to that used in the foregoing rabbit experiments. Each of 2 gibbons, ranging in weight from 5.1 to 6.8 kg, was administered the interferon into the right femoral vein (iv), the right thigh muscles (im), and under the skin in the subcapsular area (sc). Blood was drawn at appropriate intervals after injection from the left femoral vein. The serum was separated from clots and stored at −70° prior to assay. Interferon assays were performed by plaque reduction of poliovirus 1/Brunhilde in monolayers of U-amnion cells contained in 16 mm diameter plastic cells (Linbro FB16-24TC). Twofold dilution series were used; each critical dilution was assayed for percentage plaque reduction in 4 wells, and each sample was titered in duplicate to a 50% plaque reduction endpoint. Sample titers were calculated from geometric mean values. The international human interferon standard No. 69-19, designated to contain 5000 units/ml, gave a titer of 30,000 units/ml in this system. All titers were expressed as international units.

Results. Clearance rates of inoculated human leukocyte interferon from the serum of gibbons are illustrated in Fig. 1. No interferon was detected in any animal prior to injection (<0.3 $\log_{10}$ units/ml). After iv inoculation of 6.5 $\log_{10}$ units, the concentration in serum was 4.2 $\log_{10}$ units/ml 3 min later. This is an essentially complete recovery of the dose, since an estimated serum volume of 200 to 300 ml can be derived from body weight (9). The 3 min titer decreased almost exponentially for 3 hr; the half-life during the first hour was approximately 17 min. After 3 hr an obvious tailing effect was observed in the disappearance curve, providing for still measurable levels of interferon as late as 24 hr after inoculation (0.6 $\log_{10}$ units/ml). After im inoculation, moderate

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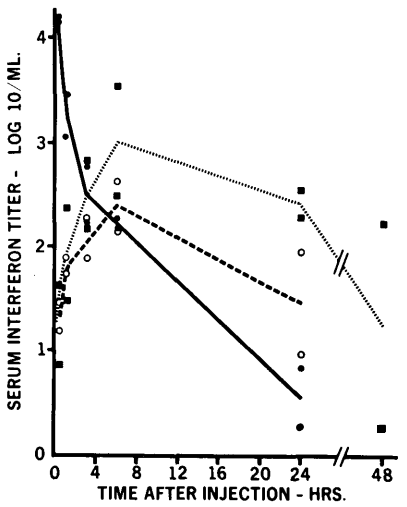

FIG. 1. Clearance of circulating human leukocyte interferon from the gibbon with time after injection of 6.5 log units. (●—) iv; (○- -) im; (■•••) sc.

levels of interferon had appeared in the serum by 15 min (1.3 $\log_{10}$ units/ml), but the peak serum concentration was not achieved until 6 hr (2.4 $\log_{10}$ units/ml). Although the maximum amounts of interferon recovered from serum was approximately 100-fold less following im than iv injection, nearly 10-fold more was apparent after 24 hr, suggesting sustained release from the tissue depot. The profile of interferon serum levels following sc administration was similar to that resulting from the im dose except that consistently higher serum levels were attained. An appreciable concentration was still evident 48 hr after injection (1.3 $\log_{10}$ units/ml).

Discussion. These data demonstrate that the characteristics of human leukocyte interferon clearance by the gibbon are comparable to the results obtained with mouse and rabbit interferons in homologous species and similar to human interferon in the rabbit. In all instances its initial half-life following iv administration is less than 20 min; attributable primarily to rapid diffusion to extravascular sites, and to tissue binding. Mouse interferon, at least, is not destroyed sufficiently rapidly by blood (2, 4), is not cleared sufficiently rapidly by the kidneys (3), and cannot be recovered in sufficient concentration from the organs (3) to account for such a drop in titer. Further, the diminishing rate of human interferon clearance in the gibbon following iv injection is observed with mouse (3, 5) and rabbit (6) interferons in homologous species and with human leukocyte interferon in the rabbit (8). Probably saturation of receptor sites or a release of bound interferon accounts for this effect. The more extended period of detection of interferon in the present study undoubtedly relates to the higher dose level used. The im and sc routes of administration provide for the maintenance of higher serum levels of interferon for a longer interval at the cost of a lower initial serum concentration. Since tissue-bound, rather than circulating, interferon should afford activity (the latter representing excess), the im or the sc route of administration might be preferred to obtain a long lasting interferon action.

Summary. Interferon clearance rates in the gibbon were compared among three different routes of administration. The results demonstrated that iv administration of human leukocyte interferon resulted in initially high serum levels and subsequent rapid clearance. In contrast, im and sc routes of administration resulted in a lower initial serum concentration, but provided for the maintenance of higher serum levels of interferon for a longer period of time.

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