Circulating Human Interferon after Intramuscular Injection into Animals and Man

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SUMMARY

Intramuscular injection of concentrated human leucocyte interferon into mice, guinea pigs, rabbits, sheep and man gave a long-lasting plateau of circulating interferon. The relation between the interferon dose and the subsequent serum level was similar in all species.

Human leucocyte interferon is rapidly cleared from the blood of rabbits and gibbons after intravenous injection, but a relatively stable serum level can be maintained for 12 to 24 h after intramuscular (i.m.) injection (Cantell & Pyhälä, 1973; Skreko et al. 1973). In current clinical trials human leucocyte interferon is being administered to patients with cancer by i.m. injection (Strander et al. 1973). This paper describes the relation between the i.m. dose of human interferon and the subsequent serum interferon level in species that differ both in size and in responsiveness to the antiviral action of human leucocyte interferon (Lockart, 1973). For the first time, circulating interferon is demonstrated in patients receiving exogenous interferon i.m.

The human leucocyte interferon was produced, concentrated and assayed as described by Cantell & Pyhälä (1973). The preparations contained $3.5 \times 10^5$ to $1.5 \times 10^6$ reference units/ml and about $50 \text{ mg/ml}$ protein.

Randomly bred animals were used and their weights were as follows: mice 35 g, guinea pigs 350 g, rabbits 3.5 kg and sheep 45 kg. Mice were injected with 0.05 ml, the guinea pigs received 0.5 ml, the rabbits 5 ml and the sheep 50 ml, divided into ten doses of 5 ml given in rapid succession. Groups of 3 to 5 mice, under ether anaesthesia, were bled with Pasteur pipettes from the axilla at different times after interferon injection and the sera were pooled for each assay sample. Repeated blood samples were taken from the same individual guinea pigs, rabbits and sheep. The guinea pigs were bled by cardiac puncture, the rabbits from the marginal ear vein and the sheep from the jugular vein. Two human patients with Hodgkin's disease, weighing 50 and 72 kg, respectively, were injected with 5 million units of interferon. The third human subject was a child with osteogenic sarcoma. Her weight was 25 kg and she received 2.5 million units. Blood samples were collected before and at intervals after the injection.

Fig. 1 shows the serum interferon levels attained in the different species. It can be seen that circulating interferon was readily detected in all species soon after the injection and that serum levels remained more or less stable for up to 12 h.

The serum interferon levels attained in the different species are compared in Table 1. The interferon dose per kg of body weight was essentially the same in the four animal species. The serum interferon levels obtained can also be regarded as similar, in view of the lack of precision of the interferon assay (threelfold differences lie close to the 95% confidence limits). The corresponding human dose was about 1/5th of the animal dose and the serum interferon levels of the three human subjects were proportionally lower. The results indicate that intramuscular injection of 200,000 to 300,000 units of human leucocyte interferon per kg
Table 1. *Relation between intramuscular interferon dose and subsequent serum interferon level in different species*

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of individuals</th>
<th>Weight (kg)</th>
<th>Interferon units injected intramuscularly</th>
<th>Interferon units injected per kg of body weight</th>
<th>Mean level of interferon units per ml of serum (1 to 12 h)</th>
<th>Calculated minimum dose per kg to attain 100 units per ml of serum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>44</td>
<td>0.035</td>
<td>17500</td>
<td>500000</td>
<td>348</td>
<td>144000</td>
</tr>
<tr>
<td>Guinea-pig</td>
<td>43</td>
<td>0.35</td>
<td>175000</td>
<td>500000</td>
<td>221</td>
<td>226000</td>
</tr>
<tr>
<td>Rabbit</td>
<td>4</td>
<td>3.5</td>
<td>1750000</td>
<td>500000</td>
<td>60</td>
<td>167000</td>
</tr>
<tr>
<td>Sheep</td>
<td>1</td>
<td>45</td>
<td>3000000</td>
<td>670000</td>
<td>168</td>
<td>338000</td>
</tr>
<tr>
<td>Man</td>
<td>3</td>
<td>50</td>
<td>500000</td>
<td>100000</td>
<td>50</td>
<td>200000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>72</td>
<td>50000000</td>
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<tr>
<td></td>
<td></td>
<td>25</td>
<td>25000000</td>
<td>100000</td>
<td>60</td>
<td>167000</td>
</tr>
</tbody>
</table>

Fig. 1. Serum interferon levels in different species after intramuscular injection of human leucocyte interferon. Each mouse point represents pooled sera from three to five animals, all other points represent individual sera.
body weight maintains about 100 interferon units per ml of plasma for about 12 h in several mammalian species, regardless of the size of the individual or the sensitivity of its cells to the antiviral action of human interferon (Lockart, 1973). We have recently found (Cantell et al. 1973) that partially purified human leucocyte interferon, although giving higher serum peaks, does not maintain the level of circulating interferon as long as the crude concentrated interferon used in this study. Further work is needed to show how the purity of exogenous interferons and their structure (Dorner, Scriba & Weil, 1973) affect clearance.

The stable plateau of serum interferon after i.m. injection is probably maintained by continual entrance and clearance of interferon from the blood. The present findings suggest that neither of the two processes is affected by whether the interferon used is homologous or heterologous. Therefore, animal experiments with human interferon are likely to provide useful information about the pharmacokinetics of human interferon in man.

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REFERENCES

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