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STUDIES ON THE SUITABILITY OF ALPHA-HYBRID INTERFERON APPLICATION IN CATTLE

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Abstract—Twelve cattle with body wts ranging from 100 to 250 kg were treated using various doses and routes for four days with an E. coli derived alpha-hybrid interferon. The lowest parenteral doses (10⁴ units per kg body wt) and the orally administered interferon did not lead to any disturbances, whereas the higher dosages led to marked changes in body temperature, pulse and respiration rates. Animals with the highest dose (10⁸ units per kg body wt) became extremely distressed. The blood picture showed distinct changes, with very low leukocyte counts during treatment, which took weeks to recover. It is suggested that the dosages that did not lead to clinical symptoms are best suited for prophylactic or therapeutic purposes.

Key words: Alpha-hybrid interferon, body weight, body temperature, pulse rate, respiratory rate, WBC, dosage.

Résultat—Douze bovins pesant entre 100 et 250 kg ont été traités par des doses et voies d'administration variées pendant quatre jours avec un interféron alpha-hybride dérivé de E. coli. Les doses les plus basses (10⁴ unités par kg du poids vif) administrées par voie orale n'ont engendré aucun trouble, tandis que les doses plus élevées causaient des modifications importantes de la température du corps ainsi du pouls et des mouvements respiratoires. Les animaux ayant reçu les doses les plus élevées (10⁸ unités par kg du poids vif) manifestaient une détresse extrême. La formule leucocytaire subissait des changements importants avec des taux leucocytaires très bas pendant les jours de traitement. Plusieurs semaines étaient nécessaires pour retrouver une formule normale. Il est suggéré que les doses n'engendrant pas des symptômes cliniques sont les mieux appropriées pour les buts prophylactiques ou thérapeutiques.

Mots-clés: Interféron alpha-hybride, poids vif, température du corps, taux du pouls, taux des mouvements respiratoires, taux leucocytaire, dosage.

INTRODUCTION

After detection and first application of interferon (IFN) an IFN-rush started. IFN was almost considered as a panacea.

Viral agents were the initiators that stimulated the various cells to produce IFN. In cattle the virus inducing the highest titers in mucous membranes of the respiratory and genital tracts was BHV1 [1], and a highly passaged avirulent strain of BHV1 [2] was for many years successfully used as a paramunity inducer to minimize the effects of crowding disease and treating bovine vaginitis [3]. These findings were later confirmed and it was shown that a ts-mutant of BHV1 also induces IFN production [4]. Differences in IFN induction in the respiratory tract of calves by three different parainfluenza-3-vaccines were described later [5]. IFN activity in the intestinal tract induced by rotavirus was also demonstrated.
Subsequently various synthetic, cell culture or bacteria derived alpha-IFNs were
developed and first tested in vitro [7–11] with positive results. However, when the IFNs
were tested in vivo different results were reported. A distinct protective effect was not
achieved with transmissible gastroenteritis virus in newborn pigs [10] and also not with
paranfluenza-3-virus in cattle [12]. Positive results were obtained in treating cattle
prophylactically against BHV1 [13], bovine virus diarrhoea virus disease [14] and vaccinia
virus infection [15] and for therapeutic reasons in rota and corona virus infections [16].
An effect on the course of a foot-and-mouth disease virus infection was also described [2].

The object of this study was to examine the effects of different doses and modes of
administration of an E. coli derived alpha-hybrid IFN which had been tested previously
in tissue cultures and orally in calves suffering from digestive tract disorders [16].

MATERIAL AND METHODS

Alpha-hybrid-IFN

The alpha-hybrid-IFN (ahIFN) was an E. coli derived purified, antibody free, slightly
modified lymphoblastoid interferon with a specific activity of $3 \times 10^9$ units per ml,
developed and provided by Hoechst AG, Frankfurt.

Animals

Twelve cattle with body weights ranging from 100 to 250 kg were parenterally or orally
treated with various doses of ahIFN as summarized in Table 1.

Clinical parameters

The white blood cell picture of all animals was determined before administration of
ahIFN, together with body temperature, pulse and respiration rates. They were repeated
immediately after the administrations and at hourly intervals, in general until 9 h later. The
white blood cell count was also determined at intervals indicated in Tables 2 and 3.

RESULTS

Body temperature

After the intravenous administration there was no increase in animals with the low dose
(Nos. 401 and 402, Table 1), but the higher doses produced a distinct elevation, with the
maximum being reached between the 3rd and 6th hour (40.8°C). Following consecutive
treatments, the increases were less marked. Only one animal (No. 435, Table 1) reached
40.8°C during the 5th hour. No difference was observed between i.v., i.m. and s.c.
administrations. Orally administered ahIFN did not produce any changes.

Pulse rate

A marked rise was only observed in those animals which received the highest dose (Nos.
435 and 436, Table 1) coinciding with the rise in temperature. The same response occurred
on the following days with no reaction in the animals treated orally.

Respiration rate

Only the lowest dose and the orally treated animals failed to exhibit a distinct rise, but
all the others reacted with a marked increase. Animal No. 427 started, for example, with
a rate of 32/min and reached 106 after 2 h and No. 436 started with a rate of 30/min which
increased to 104 after 2 h. After repeated administrations the effect was less dramatic and independent of the route of administration.

**White blood picture**

*Leukocytes.* The leukocyte number was lower in all animals except those which received the lowest parenteral and oral doses. The greater the dose the faster the reduction. The same effect occurred after subsequent injections. Immediately after the reduction started an increase which reached and exceeded levels approx. 9 h after administration. The lowest count (1000 leukocytes/μl) occurred in animal No. 435 3 h after the second administration.

*Differential WBC counts.* There was no obvious effect in the majority of animals. An initial reduction in lymphocytes was followed by a reduction in neutrophils. A similar picture was observed in the weeks following administration. A summary of the changes is shown in Tables 2 and 3.

**Other clinical signs**

These were observed in the 2 animals (Nos. 435 and 436, Table 1), which received the highest dose. In summary, No. 435, increased serious nasal discharge 3 h after the first injection, still present on day 2, but with laboured breathing and anorexia 2 h later. Increased salivation 1 h after the third treatment. Animal No. 436, trembling and cough

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### Table 1. Body wt, ahlFN doses and route of application in 12 cattle

| Animal no | Body wt (kg) | Dose (per kg in units) | Days and route of application |
|-----------|-------------|------------------------|-------------------------------|
| 401       | 250         | $10^4$                 | i.v. i.v. i.m. i.m.           |
| 402       | 250         | $10^4$                 | i.v. i.m. i.v. i.m.           |
| 403       | 250         | $10^5$                 | i.v. i.v. i.m. i.m.           |
| 419       | 250         | $10^5$                 | i.v. i.m. i.v. i.m.           |
| 427       | 100         | $10^3$                 | i.v. i.v. i.m. i.m.           |
| 429       | 100         | $10^3$                 | i.v. i.m. i.v. s.c.           |
| 435       | 100         | $10^6$                 | i.v. i.v. s.c. i.m.           |
| 436       | 100         | $10^6$                 | i.v. i.m. i.m. i.v.           |
| 453       | 200         | $5\times10^5$          | p.o. p.o. p.o. p.o.           |
| 454       | 200         | $5\times10^5$          | p.o. p.o. p.o. p.o.           |
| 455       | 200         | $5\times10^6$          | p.o. p.o. p.o. p.o.           |
| 456       | 200         | $5\times10^6$          | p.o. p.o. p.o. p.o.           |

i.v., intravenously; i.m., intramuscularly; s.c., subcutaneously; p.o., orally in gelatinous capsules.

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### Table 2. Leukocyte counts before first administration of ahlFN, 1 day, 1 week, 2 and 4 weeks after the last injection per mm$^3$ of blood

| Animal no | Before | 1 Day | 1 Week | 2 Weeks | 4 Weeks after |
|-----------|--------|-------|--------|---------|---------------|
| 403       | 5400   | 4300  | 3900   | 4700    | 3800          |
| 419       | 11,800 | 7800  | 7600   | 12,800  | 7800          |
| 427       | 8100   | 11,100| 11,100 | 10,600  | 10,800        |
| 429       | 5100   | 6100  | 5400   | 1800    | 7700          |
| 430       | 6100   | 5400  | 5500   | 7500    | 6300          |
| 436       | 8500   | 6600  | 9700   | 8600    | 8100          |
Table 3. Absolute numbers of neutrophils (N) and lymphocytes (L) before first administration of ahIFN, 1 day, 1 week, 2 and 4 weeks after the last injection per mm$^3$ of blood

| Animal No | Before | 1 Day | 1 Week | 2 Weeks | 4 Weeks after |
|-----------|--------|-------|--------|---------|---------------|
|           | N      | L     | N      | L       | N             | L             |
| 403       | 1350   | 3888  | 473    | 3612    | 507           | 3525          |
| 419       | 3422   | 7906  | 5694   | 5472    | 2032          | 8763          |
| 427       | 1458   | 6561  | 5328   | 5550    | 5512          | 5088          |
| 429       | 1275   | 3774  | 4941   | 3510    | 234           | 1548          |
| 435       | 1368   | 4392  | 4644   | 1950    | 5100          | 1827          |
| 436       | 1530   | 6885  | 594    | 6984    | 2064          | 6336          |

after 1 h and a foamy nasal discharge after 2 h; no other signs were observed after the other injections.

DISCUSSION

The oral administration of $1 \times 2 \times 10^6$ or parenteral injection of $10^4$ units ahIFN/kg body wt did not lead to any disturbances. Hofmann et al. [16] used approximately the same dose for the treatment of digestive disorders in calves. It seems most likely therefore that the positive results can be attributed to the treatment, since this could substantiate the efficacy of ahIFN treatment in vitro and in vivo with rota- and coronaviruses. However, higher doses certainly do more harm than good, and not only for short periods of time as judged by the clinical signs, but for long periods of time, as is evident from the changes in the white blood picture. The route of parenteral administration does not seem to be relevant. The same is obviously true for the body weight resp. age. The results are in general agreement with those obtained by Gillespie and coworkers [17].

It is not unexpected that IFN administration does not influence PI3-virus infections [12], as PI3-virus induces IFN activity [5]. The same is true for BHV1 [1]. Therefore, there is no justification to administer IFN prior to BHV1 exposure [13]. The results are encouraging concerning BVDV infections [14]. If IFN acts as an immunostimulant [13], it could be used to improve the immune response, especially following the vaccination with inactivated BVDV vaccines.

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