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

OTTO CHRISTIAN STRAUB
BFAV, P.O. Box 1149, D-72001 Tübingen, Germany

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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 (10^4 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 (10^8 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.

Résumé—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 dérivée de *E. coli*. Les doses les plus basses (10^4 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 (10^8 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 symptomes cliniques sont les mieux appropriés pour les buts prophylactiques ou thérapeutiques.

Mots-clefs: 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

[6]. 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 3×10^8 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

Table 1. Body wt, ahIFN doses and route of appliction in 12 cattle

Animal no.	Body wt (kg)	Dose (per kg in units)	Days and route of application 1	2	3	4
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	10^5	i.v.	i.v.	i.m.	i.m.
429	100	10^5	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	$5–10 \times 10^5$	p.o.	p.o.	p.o.	p.o.
454	200	$5–10 \times 10^5$	p.o.	p.o.	p.o.	p.o.
455	200	$5–10 \times 10^6$	p.o.	p.o.	p.o.	p.o.
456	200	$5–10 \times 10^6$	p.o.	p.o.	p.o.	p.o.

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

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

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

Animal no	Number of leukocytes per μl of blood: Before	1 Day	1 Week	2 Weeks	4 Weeks after
			Injections of ahIFN		
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.	Absolute numbers of neurophils (N) and lymphocytes (L)									
	Before		1 Day		1 Week		2 Weeks		4 Weeks after	
	ahIFN injections									
	N	L	N	L	N	L	N	L	N	L
403	1350	3888	473	3612	507	3354	1034	3525	874	2698
419	3422	7906	1482	5694	1216	5472	2032	8763	1404	6240
427	1458	6561	5328	5772	5328	5550	5512	5088	4578	6213
429	1275	3774	1098	4941	1890	3510	234	1548	2772	4697
435	1586	4392	756	4644	2035	3465	1950	5100	1827	4284
436	1530	6885	594	5940	2716	6984	2064	6536	1620	6399

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 $1–2 \times 10^6$ 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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