DEVELOPMENT OF INTRANASAL VACCINATION FOR THE IMMUNIZATION OF CATTLE AGAINST INFECTIOUS BOVINE RHINOTRACHEITIS

J. D. Todd*

RESEARCH CONDUCTED AT JENSEN-SALSBERY LABORATORIES in 1968 and 1969 resulted in the development of an intranasal vaccine for the prevention of parainfluenza type 3 (PI-3) virus infection in cattle. Development of that vaccine was based on the concept that the bovine immune defense system was analogous to those of other animal species, including man, in which the secretory immune system had been shown to consist of local (external secretory) as well as systemic (internal secretory or circulating) antibody components. Investigations carried out since that time by several research groups throughout the world have shown unequivocally that the bovine immune mechanism is indeed analogous to those of other species in respect to its being comprised of both local and systemic antibody responses to infection. These studies have confirmed that bovine external secretory antibodies belong predominantly to the immunoglobulin class A (IgA), in contrast to circulating antibodies which are predominantly of immunoglobulin classes G, IgG and IgM. They also support the earlier findings that external secretory antibody production is most readily initiated by local application of antigen.

Evaluation of field and experimental data revealed the existence of a critical balance between the safety and potency of attenuated infectious bovine rhinotracheitis (IBR) virus for use as an intramuscular vaccine. It was found that IBR virus which had been too highly attenuated did not promote an adequate antibody response following administration by the intramuscular route. Virus which had been attenuated only slightly was found to produce a good circulating antibody response, but retained the potential to cause respiratory disease if administered by the respiratory route. In addition, IBR vaccines which were effective when given by the intramuscular route could not be administered to pregnant cows because of the danger of fetal infection resulting in abortion. The need for a vaccine possessing increased safety and the capacity to stimulate a more effective protective response became apparent.

The development of an IBR vaccine for *intranasal* administration was initiated for two principal reasons: a) A higher level of attenuation (for safety) could be achieved since the natural route of infection was to be used as the route of inoculation and b) a complete host response (immune and nonimmune factors) against respiratory infection could be promoted by administration of vaccine virus by the respiratory route.

The intranasal vaccine strain of the IBR virus was selected by serial passages of virus in cultured cells of a heterologous (lapine) species after having been passaged over 50 times in cultured cells of bovine origin. The seed cultures of IBR virus used for the production of vaccine were derived by multiple cloning procedures to select the virus type most completely adapted to the heterologous cell system, thus presumably the most attenuated for the bovine.

Numerous controlled laboratory and field studies were conducted to evaluate safety, efficacy, and host response factors following intranasal administration of the selected, avirulent strain of IBR (AV-IBR) virus alone, and in combination with the *TELC*™ strain of PI-3 virus (Nasalgen IP). A portion of these studies are summarized below.

1. Fifty-four calves, including eight colostrum-deprived calves, were vaccinated intranasally with AV-IBR virus during preliminary investigations. There was no evidence of clinical illness among vaccinates, and calves responded with circulating antibody titers higher than expected with intramuscular IBR vaccine. These studies provide early evidence of vaccine safety and potency.

2. Groups of calves were vaccinated with intranasal AV-IBR virus and were then challenged with virulent IBR virus 18, 40, 72, or 96 hours later to determine how soon resistance to challenge would develop. Calves challenged at 18 or 40 hours developed clinical disease whereas those

*Research Department, Jensen-Salsbery Laboratories, Division of Richardson-Merrell Incorporated, Kansas City, Missouri 64141.

challenged at 72 or 96 hours were protected. The onset of protection occurred, therefore, at some point between 40 and 72 hours after vaccination. Interferon was present at low levels in nasal secretions of a small percentage of calves at 40 hours, but was present at high levels in all calves evaluated at 72 hours.

3. Studies conducted to evaluate the relationships between vaccine virus replication, interferon induction, and antibody response has provided the following information.

   a) Virus replication in cells of the respiratory tract continues from time of vaccination until about the tenth day post vaccination.
   b) Interferon first becomes detectable in respiratory tract secretions 40 to 48 hours after vaccination, and reaches high levels at 60 to 72 hours. These high levels are then maintained for six to eight days, or as long as active virus replication continues.
   c) Circulating interferon is present at low levels in the serum from about the fourth through seventh days postvaccination.
   d) The amount of virus present in respiratory tract secretions is reduced by over 99% coincident with the appearance of peak levels of interferon in the secretions.
   e) Circulating antibody first becomes detectable on about the eighth day postvaccination, and reaches maximal levels by the 14th to 17th days.
   f) Ultimate disappearance of detectable virus coincides with the appearance of circulating antibody.
   g) Antibody against IBR virus was found postvaccination in nasal secretions of calves vaccinated by the intranasal route but not in calves vaccinated by the intramuscular route.
   h) No interferon was detected in either nasal secretions or serum of calves which received intramuscular IBR vaccine.

4. Nasalgen IP vaccine was administered to groups of calves to evaluate onset of protection against IBR challenge virus, and to determine the compatibility of the AV-IBR and TELC™ PI-3 viruses in combination.
   a) Calves were found to be resistant to IBR challenge as early as 48 hours postvaccination.
   b) Interferon levels resulting from the AV-IBR virus fraction were as high and persisted as long following administration of the IBR/PI-3 combination as had been demonstrated following administration of intranasal AV-IBR virus alone.
   c) All calves vaccinated developed secretory antibody against both IBR and PI-3 viruses, and all developed high levels of circulating antibody against both viruses.

5. Intranasal AV-IBR virus was administered to 156, and Nasalgen IP to 150, IBR-susceptible cows in varying stages of gestation. All animals were evaluated for adverse effects, including abortion, for at least 90 days postvaccination. One hundred twenty-nine (129) IBR-immune, pregnant cows were also vaccinated with Nasalgen IP or intranasal AV-IBR vaccine. No IBR abortions occurred. There were seven fetal losses among the 435 pregnant vaccinates (1.6%). Four losses occurred among the 306 IBR-susceptible vaccinates (1.3%), compared to three losses among the 129 IBR-immune vaccinates (2.3%). Loss percentages among all vaccinates were lower than the normal expectancy of losses of undetermined cause. None of the calves born to AV-IBR or Nasalgen IP vaccinates were diseased at the time of birth or during the neonatal period. These studies thus affirmed the safety of both intranasal AV-IBR vaccine and Nasalgen IP for use in IBR-susceptible, pregnant cows without fear of abortion or neonatal disease.

6. Two studies were conducted to determine the potential of AV-IBR vaccine virus to revert to virulence when transferred by direct intranasal inoculation to series of IBR-susceptible animals. Ten serial passages were made in each of the two studies, using two calves for each passage. The tenth passage was conducted with IBR-susceptible, pregnant cows. No reversion to virulence occurred in either of the studies. No abortions occurred among the cows, and there were no cases of neonatal disease among their calves subsequently delivered.

7. Intranasal AV-IBR vaccine and Nasalgen IP were tested under feedlot conditions in 2,761 calves. Under these conditions both vaccines proved to be both safe and efficacious. The overall incidence of respiratory disease among these vaccinates was lower than in control groups of calves which received intramuscular IBR vaccine.

All studies conducted to date with intranasal AV-IBR vaccine and Nasalgen IP are in agreement with the conclusion that these vaccines provide degrees of safety and efficacy not previously available to the bovine industry. Because of the unusual safety demonstrated in pregnant cows, both vaccines have been approved by the USDA for use in these animals. Ramifications of the number of potential uses which may be made of the intranasal IBR vaccines for interferon induction in preventing or reducing severity of many bovine respiratory infections of virus etiology have yet to be explored.

ANALYSE DE VOLUME

Cat Anatomy. An Atlas, Text and Dissection Guide. R. C. McClure, M. J. Dallman et P. G. Garrett. Publié par Lee & Febiger, Philadelphia. 1973. Vendu au Canada par Macmillan, Toronto. 240 pages. Prix $10.75

Anatomistes de carrière, les auteurs connaissaient mieux que quiconque les lacunes qui existaient sur l'anatomie du chat. C'était presqu'un défi à relever que de rédiger un autre volume sur l'anatomie du chat qui fut à la fois un traité, un atlas et un guide de dissection.

Ce nouveau livre semble bien répondre à la conception rénovée de l'anatomie, le texte ne fait pas appel aux longues descriptions mais à une concision chère à la nouvelle école des anatomistes. Les dessins n'ont rien de la magie de la couleur mais ils sont quand même clairs et la précision y est constante. Les lignes paraissent avoir été tracées d'un premier jet, pourtant elles dénotent les aptitudes et le souci du détail de l'anatomiste Garrett.

La nomenclature scientifique y est respectée et confère à ce livre une portée universelle.

On ne s'attendait pas à une simple énumération de traits superficiels de la part de l'équipe dirigée par McClure, les anatomistes lui connaissent sa valeur d'enseignant et son intérêt pour les particularités.

C'est d'abord un livre qui sera fortement recommandé aux étudiants en médecine vétérinaire, il aura aussi sa place dans la bibliothèque des vétérinaires cliniciens des petits animaux qui y référeront fréquemment.

L'Appendice I est une sorte de tableau synoptique qui servira d'aide-mémoire aux étudiants, l'appendice II sera encore d'un grand intérêt pour les cliniciens, la bibliographie pourra être utile à tous. Je vous le recommande. *O. Garon.*

ABSTRACT

Occurrence of mastitis during the dry period and early lactation. G. E. Ward (West. Coll. Vet. Med., Saskatoon, Sask.).

Cows (402) were examined one week before drying-off; on the day of drying-off; one, two and three weeks after drying-off; and at parturition, and one, two and four weeks after parturition for the occurrence of mastitis. Alternate cows were infused with antibiotics (500 mg neomycin) at drying-off. Most new infections established during the first week of the dry period (24 quarters/100 cows in cows not receiving antibiotic therapy and 5 quarters/100 cows in cows receiving antibiotic therapy at drying-off). During the remainder of the dry period new infections occurred at the rate of 5 quarters/100 cows/week in all cows. At parturition 11 quarters/100 cows and 16 quarters/100 cows developed new infections in antibiotic treated and untreated groups respectively. At 4 weeks post-partum new infections occurred at the rate of <4 quarters/100 cows in both groups. Streptococcal infections were most frequently established in the early dry period and staphylococcal most frequently at calving. Abnormal swelling and secretion occurred more frequently during the first week of the dry period and the first week of lactation. New infections were esablished in cows with other quarters already infected in 6 of 7 *S. agalactiae*, 8 of 56 *S. uberis*, 8 of 39 *S. aureus*, and 1 of 18 Gram-negative rod infections.

The percentage of cows infected with streptococci was higher in older cows than in younger cows but was similar in all age groups for *S. aureus*. The yield of milk just prior to drying-off did not significantly affect the number of new infections established during the dry period.

Research Rostrum of the Twenty-fifth Canadian Veterinary Medical Association Annual Convention, Edmonton, Alberta 1973.