ADVANCES IN BHV1 (IBR) RESEARCH

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ABSTRACT

Bovine Herpesvirus Type 1 (BHV1) is the aetiological agent of a number of diseases and not only of IBR, namely infectious pustular vulvovaginitis IPV), infectious balanoposthitis (IBP), conjunctivitis, encephalomyelitis, mastitis, abortion, enteritis, and lesions in the interdigital space. The serological identical strains differ, however, in same aspects. Typical genital strains usually cause a mild illness, sometimes not even detected clinically, but serologically. They hamper eradication programmes and do not cause IBR when intranasally inoculated. The other – modern – strains are, however, always able to induce a severe disease in the genital tracts. But infection of field or vaccine virus leads to the development of humoral and cell-mediated immunity. The latter is, however, not transmitted to neonates via colostrum.
BHV1 antibodies can be found in all continents and also in many other, especially wild species. Prevalences vary greatly depending on herd size and management.

Because seronegative cattle play a role in international trade a number of European countries have eradicated BHV1 with the very high costs involved.
Marker and conventional vaccines can prevent disease but not infection followed by the state of latency. More than one strain including marker vaccines can remain latent in the same animal and be shed after stress or injection of corticosteroids.
For the detection of humoral antibodies the ELISA is widely used. It works in bulk milk samples for antibodies derived from field virus and conventional vaccines but not from gE-deleted marker vaccine.

Importing countries should take care that only vaccinated animals are imported. They may require that the animals are seronegative prior to vaccination

Introduction

IBR means Infectious Bovine Rhinotracheitis in nomenclature introduced in 1955 in the USA to describe a new disease previously called “Red Nose Disease” or “Infectious Necrotizing Rhinotracheitis”. It occurred mainly in feedlots and large dairy herds and was highly contagious. At that time it was not known that the viruses causing Infectious Pustular Vulvovaginitis (IPV) and Infectious Balanoposthitis (IPB) were serologically identical. Later more conditions were found to be caused by the IBR-IPV-IBP-virus such as abortion, encephalomyelitis - mainly in calves but recently also in an adult cow (Roels et al., 2000) -, mastitis, enteritis, conjunctivitis and lesions in the interdigital space. Since the virus was then identified as a member of the

herpesvirus family it became Bovine Herpes Virus (BHV) and being the first of a group of bovine herpesviruses the type 1 (BHV1). By molecular biological studies the BHV1 viruses were again divided into subgroups such as BHV1.1, BHV 1.2. etc. Lately the closely related agent causing encephalitis mainly in South America and Australia was named BHV5. Both, BHV1 and BHV5 have recently been described as aetiological agents of encephalomyelitis by Meyer et al. (2000). Differences in the antibody levels could, however, be found (Teixeira et al, 1998). In the following knowledge accumulated in BHV1 studies is presented.

Host range and geographic distribution

Data published in 1990 (Straub) were confirmed by reports that cattle checked for BHV1 antibodies in any country or island such as Reunion or the Adaman (Shome et al.,1997) were found to be positive except Island. But in the meantime countries such as Denmark, Sweden, Finland, Switzerland, parts of Austria and Italy are officially recognised as free of BHV1 following strict sanitary measures. The host range was increased by reports from India and Italy on buffaloes (Rao & Char, 1991; Guarino et al.,1999) and on Asian elephants (Bhat et al., 1997). Closer examination of the virus isolated from reindeer revealed that it is not BHV1 but rather a separate herpes virus species (Rimstad et al., 1999). A summary of various hosts was presented 1990 (Straub). It included ferrets, rabbits, skunks, hamsters, goats and sheep.

Prevalences

In countries like the USA and Canada where cattle are routinely vaccinated it is impossible to determine the prevalences. In Italy for example 47% of breeding cattle from 473 non-vaccinated herds were seronegative and 55% from 139 vaccinated herds seropositive (Nardelli et al., 1999). In other parts of Italy the rates were 84,31 and 100% (Castrucci et al.,1997). In Poland they recorded in one region 20,6 in another 37,9% seropositivity in dairy cattle (Rola & Zmudinski, 1999). In Hungary the prevalence in large herds was 64,1 and in small herds 15,7%. Interestingly the prevalence in small herds neighbouring large herds was higher than in isolated small herds (Tekes et al., 1999). A survey conducted in parts of Brazil revealed 41,9 % of 506 sera BHV1 seropositive whereas in Argentina in cases of meningoencephalitis in calves only 17 % were seropositive against BHV1 (Marin & Campero, 1999; Langoni et al., 1999). In New Zealand 66,54% of the cattle had antibodies against BHV1 (Motha & Hansen, 1998).

Clinical symptoms and virus excretion

In most cases the clinical symptoms are so distinct that they cannot be overlooked with one exception. Typical genital BHV1 strains may pass through a whole herd of cattle without being noticed by the herdsman. Especially in countries where eradication programmes are conducted serum or bulk milk examinations reveal that an infection must have struck the animals without clinical symptoms. **It must always be kept in mind that these low virulent strains never cause IBR but any IBR strain is capable of causing severe clinical symptoms in the genital tracts of heifers, cows and bulls**. Bulls continue to serve females or produce semen full of virus before severe lesions in the prepuce stop them from serving. Virus excretion lasts in general about two weeks, and its maximum around three weeks after the first infection. This is also true for the excretion of live attenuated vaccines applied onto the mucous membranes of respiratory and/or genital tract. Interesting in this context was the report which showed how social isolation may influence responsiveness to

infection in calves. Cortisol levels increased and clinical symptoms diminished, virus shedding and antibody production were somewhat delayed (van Reenen et al., 2000).

Humoral and cell mediated immunity

Following an infection or vaccination both types of immunity are induced and can be used for diagnostic purposes. Important to know is only that cell-mediated immunity is not transferred to newborns via colostrum. An intradermal test will therefore give a negative result and is able to differentiate between an active and passive acquired immunity (Wizigmann et al., 1989). Which role the various glycoproteins play in the induction of the cell-mediated immunity was examined by Denis et al. (1996).

Vaccines

The first vaccines were developed fairly soon after the identification of the causative virus of IBR in the USA on the market. Most of them were live, but frequently not properly attenuated leading for example to a vaccine that did not offer protection against IBR but induced abortions (Straub, 1990). All of them were administered parenterally and appeared therefore to be safe. This changed in 1970 when a first report described the local vaccination onto the mucous membranes of respiratory and genital tract with a truly attenuated live vaccine (Straub, 1970/1971). For more than 25 years live attenuated and ts-mutant as well as inactivated and subunit vaccines were commercially produced and widely used in many countries, where BHV1 infections were responsible for severe losses be it loss of milk production, emaciation or mortality. The new techniques in molecular biology lead to the development of a number of experimental vaccines. Examples: recombinant vaccines – basis baculo- or vaccinia virus - , an intradermal applicable BHV1 DNA vaccine, a gene gun with a plasmid expressing a truncated, secreted form of BHV1 glycoprotein D and a TK gene lacking vaccine (Straub, 1991; Miller et al., 1991; Drunen Little-Van den Hurk et al.,1993 and 1998; Chowdhury,1996; Braun, et al.,1999). None of them ever went into commercial production.

A breakthrough was achieved when gene-deleted vaccines were developed. Two of them a gE- and a gG-deleted and a gD-subunit vaccine were tested in field trials. Each of them exhibited special advances but the final conclusion was made in favour of the gE-deleted vaccine, when the live form gave the best results concerning protection from BHV1 induced disease (Bosch et al., 1996; Straub, 1999). This gE-deleted vaccine is now commercially produced and provides the basis for the eradication programmes conducted in most countries of the European Union. The main advantage is the possibility to differentiate the antibodies from those induced by field or conventional vaccine virus. But for feedlot cattle conventional vaccines are still licensed. In the other continents conventional BHV1 vaccines live and inactivated and frequently combined with other viral antigens are most common.

Numerous studies have been conducted with this gE-deleted vaccine distributed now by the German Bayer and the Dutch Intervet Company. They can be summarised as follows:

The intranasal application of the live vaccine proved to give almost the same results obtained with the conventional attenuated live one. The vaccine virus was shed maximally until day 16 post vacc. A second vaccination 4 or 7 weeks later led to a minimal shedding of vaccine virus in the minority of the animals , thereby demonstrating the strength of the local immunity. When vaccinated cattle were

challenged by neighbouring field virus, inoculated animals did not show any symptoms of IBR, whereas the non-vaccinates developed severe IBR (Straub, 1999). In another experiment Makoschey and Keil (2000) could show that the protection was also strong after the intramuscular administration of the vaccine and as early as three days after intranasal and seven days after intramuscular injection a reduction of the shedding of challenge virus was documented. Only one minor disadvantage occurred when the inactivated form of gE-deleted vaccine was injected into milking cows. Their milk production decreased, after a double vaccination, significantly 1.4 l per cow and day for the first six days (Bosch et al., 1997).
Ellis et al. (1996) report that it is still advantageous to vaccinate newborn calves in the presence of maternal antibodies with live vaccine, because the animal's immune system is primed to recognise viral antigens.

Latency
Sheffy and Davies were the first to describe the phenomenon of latency in 1972. It is this property of herpesviruses that markedly hampers BHV1 control. The genome of the various BHV1 strains as is well known persists lifelong in the ganglia of the tracts where BHV1 entered the body (Straub, 1998). Latency occurs in both respiratory and genital tract only if BHV1 is in contrast injected intravenously to the natural pathways (Whetstone et al., 1989). BHV1 is assembled and shed after stress or the administration of corticosteroids. It was documented that reactivation and virus shedding varies in length and intensity depending on type and dosage of corticosteroids and on the intervals between applications (Straub & Lorenz, 1991). Experiments demonstrated also clearly that more than one virus strain can become latent and be shed including the gE-deleted vaccine strain in fairly high quantities in contrast to another experiment (Bruchhof & Straub, 1993; Straub, 1999; Mars et al., 2000). Preliminary data suggested that infectious virus is shed when the immunoglobulin A levels decrease in the nasal mucus due to an increase in cortisol levels following stress of the application of corticosteroids (Straub, unpublished).

Virus isolation and antigen detection
Tissue cultures are still a valuable tool to isolate BHV1. But polymerase chain reaction (PCR) offers new possibilities for example to detect BHV1 antigen in bull semen (Rola & Zmudzinski, 1999b; Smits et al., 2000) or in peripheral blood lymphocytes (Rziha et al., 1999).

Detection of antibodies in blood and milk serum
While the conventional serum neutralisation test is still possible the ELISA is meanwhile common practice. Its sensitivity has been demonstrated in bull milk testing, but also its limitation. If, for example, a BHV1 positive animal is introduced even into a small size BHV1 negative herd, the ELISA won't detect it. It becomes only possible after more animals have been infected (Frankena et al., 1997). A draw back is also the fact that in animals vaccinated with the gE-deleted vaccine the bulk milk ELISA is not working, therefore individual blood or milk serum samples must be taken (Hartmann et al.,1997).

BHV1 in connection with artificial insemination and embryo transfer
In countries with high BHV1 infection rates methods have been developed to inactivate possible BHV1 contamination in semen by hyperimmune egg yolk semen

extender and trypsin was employed to inactivate BHV1 in embryos (Bielanski et al., 1997; Silva et al., 2000).

The role of the BHV1 glycoproteins

Lately a number of papers describe the role the various glycoproteins play in penetration and propagation in cell cultures (Meyer et al., 1998), for the infectivity (Schröder & Keil, 1999), for complex formation of gE with gI (Tyborowska et al., 2000) and the induction of cell mediated immunity (Denis et al.,1996).

The combat of BHV1

Some countries are already BHV1 free. This goal has been achieved by stringent measures and enormous costs. The eradication in Switzerland has in detail been described (Riggenbach,1998). Cost-Benefit-Analyses are very hard to show a positive relation, because most diseases caused by BHV1 can be controlled by consequent inexpensive vaccination schemes and in some countries IBR does not even play a role. Only the seroreactors demonstrate that BHV1 is present. There is therefore no doubt that the whole combat is based on export chances. Even third world countries ask for BHV1 free imports which then become infected shortly after arrival by the ubiquitous BHV1 and often severely sick since they are fully susceptible. How high a financial loss due to a lower milk production occurs has been studied on a model in the Netherlands which amounted to 0,92 kg milk/cow per day for nine weeks (Schaik et al., 1999).

A BHV1 free cattle population can also be obtained by replacing the field BHV1 gradually by vaccinating the whole population continuously with live vaccines for a number of years, preferably onto the mucous membranes of respiratory and genital tract. By the time the oldest animal, that has been vaccinated at the beginning of the programmes has left the premises vaccination can be stopped. This scheme has shown its efficacy in a large number of insemination centres. It is then not necessary to check the herds routinely for the presence of antibodies. This examination can be limited to those herds officially recognised as BHV1 free in order to maintain their negative status.

DISCUSSION

Based on the present knowledge the following points appear noteworthy:

- marker vaccines make it possible to differentiate humoral antibodies whether they are derived from field or from vaccine virus and are therefore helpful in eradication programmes
- a drawback is that the ELISA is only applicable for individual samples not for bulk milk samples as for the proof of field BHV1 or antibodies raised after the use of conventional vaccines
- all licensed vaccines are able to prevent disease
- no vaccine is able to prevent infection followed by latency .

This latter statement could not be confirmed by Mars et al.(2000). On the other hand it has been shown above how important in such trials the types and dosages of the corticosteroids and the intervals of applications are. After all gE-deleted BHV1s are still herpesviruses and this fact should always be kept in mind.

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