Adverse Effects of Inactivated Foot-and-Mouth Disease Vaccine—Possible Causes Analysis and Countermeasures

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Abstract

Foot-and-mouth disease (FMD) is an infectious and sometimes fatal viral disease that affects cloven-hoofed animals, and Chinese government adopts compulsory immunization measures for FMD. The adverse effects of FMD vaccine to pigs, cattle and goats have been reported increasingly frequent during the spring and autumn seasons when large numbers of farm livestock are vaccinated. The financial losses caused by vaccine adverse effects have been a serious concern for both farmers and primary prevention personnel. There are various causative factors reported to involve into adverse effect of FMD vaccine, including the inappropriate vaccine production, transportation and storage, livestock poor tolerance, and unqualified vaccinating manipulations. Symptomatic treatment and early drug prevention have a certain effect on the adverse effects. To analyze causes and propose countermeasures, in the current study possible reasons during the production and processing procedures of inactivated FMD vaccine were reviewed and corresponding countermeasures were recommended. The review may provide references for better use of vaccine to prevent FMD.

Keywords

Foot-and-Mouth Disease, Inactivated Vaccine, Adverse Effects, Causes Analysis and Countermeasures

1. Introduction

The adverse effects of inactivated foot-and-mouth disease vaccine are usually classified into common responses and allergic responses by instruction of manufactures. The common responses include local swelling at injection site, fever,
and gastric disorder, which will be disappeared after one or two days. Allergic reactions could be observed in vaccinated animals attributable to breed and healthy condition of each individual, manifested as anxiety, rapid breathing, muscle tremors, foaming at the mouth, and nasal bleeding; and it could be fatal without timely treatment, or lead to miscarriage by pregnant pigs. The other adverse effect such as injection site malabsorption could be observed in the animals just after vaccination for a short-term period. The adverse effects of foot-and-mouth disease (FMD) vaccine is non-negligible and it has been reported that the post-vaccination allergic reaction and mortality were 0.23% and 0.14% in cattle, 0.24% and 0.33% in dairy cows, 0.14% and 0.009% in goats, 0.08% and 0.007% in pigs, respectively (data not published).

The post-vaccination adverse effects are classified into mild, moderate and severe degree in terms of severity [1] [2] [3]; or classified into local, systematic and allergic reactions [4] [5] [6] regarding to the affected area of body. Adverse events following immunization (AEFI) has been classified into five major categories by World Health Organization (WHO) [7] [8]: 1) intrinsic to the vaccine, or may be caused by the way it is administered or be related to an underlying condition in the recipient; 2) program-related, result from inappropriate practices in the provision of vaccination; 3) coincidental AEFI, not true adverse reactions to immunizations or vaccines but are only linked because of the timing of their occurrence; 4) injection site reaction, acute stress reactions to inject; 5) undefined AEFIs which there is insufficient evidence to classify as one of the above. And the adverse effects of inactivated FMD vaccination are grouped into four major categories: 1) intrinsic to the vaccine; 2) inappropriate practices in the provision of vaccination; 3) related to an underlying disease condition in the recipient animal; 4) inappropriate route, site or technique of administration.

It is worthwhile to think about why the adverse effects are relatively less when immunization of other types of virus vaccine compared with FMD vaccine, both of which are oil-emulsion inactivated vaccines and performed by the identical personnel? The production procedure of inactivated FMD vaccine is described as “cell culture - virus proliferation - virus inactivation - oil emulsion - vaccine packing”, and what kind of addition might result in the adverse effects? Though there is no absolute safety for any types of vaccine, and adverse effects will inevitably occur with expected ratio; then thus what kind of countermeasures could be carried out before and after FMD vaccine immunization? The adverse effect might be able to significantly reduce and minimize with in-depth analysis of causes and timely application of remedial measures.

2. Causes Analysis

The virus responsible for the FMD (FMDV) is a picornavirus belonging to positive-stranded RNA viruses, with full length genome RNA of 8.5 Kb consisting 5’-untranslated region (5’ UTR), open reading frame (ORF), 3’-untranslated region (3’ UTR) and PolyA at the tail. A large numbers of structural and
non-structural proteins are produced by virus elements during viral replication and all of these products will elicit adverse reaction once being injected into recipient animals.

2.1. BHK-21 Production Cell

BHK-21 is a hamster derived cell line and commonly used for FMD vaccine production [9]. The endogenous proteins produced and secreted by BHK-21 cells, as a kind of heterologous proteins to immune recipients, and induce immune response but non-related to vaccine per se.

2.2. Newborn Bovine Serum

Newborn bovine serum is one of nature components in cell culture medium, and it provides growth factors and low molecular nutrients for adhesive cells to maintain exponential growth. A large amount of newborn bovine serum is required for growth and passage of BHK-21 cells. The major components of newborn bovine serum include albumin, globulin, α2 macroglobulin, and small amount of growth factors and hormones such as platelet growth factor, epidermal growth factor, nerve growth factor, insulin-like growth factor, insulin, and somatropin. All of these heterologous proteins from newborn bovine serum might induce a series of adverse responses [10] if they are not completely removed during vaccine purification.

2.3. Antibiotics, Trypsin, and Ethylenediaminetetraacetic acid

Antibiotics are usually added into culture medium in the large-scaled cell culture process, in order to prevent bacterial contamination. Penicillin and streptomycin are most common and conventional antibiotics; besides, kanamycin, gentamicin and amphotericin B are occasionally added into culture medium. The addition of antibiotics reduces bacterial contaminations and meanwhile increases the risk of adverse effect. For instance, penicillin, as a hapten to stimulate IgE production [11], adheres to mast cells located around the microvascular walls of bronchial mucosa and skin or attaches to basophil surface in peripheral blood, which potentially makes recipient animals in a sensitized status to one specific antigen; and the allergic reaction will be triggered once the identical antigen is encountered where the histamine is released from ruptured cells after antigen binding to IgE [12], with the results of smooth muscle contraction, telangiectasia, and increased vascular permeability. Streptomycin can cause allergic reactions, ototoxicity and renal toxicity similar to penicillin, but relatively occasionally. Trypsin is proteolytic enzyme, extracted from pancreas of cattle, goat or pig; and selectively hydrolyzes polypeptide composed of lysine or arginine, widely used in the cell passage manipulations. And ethylenediaminetetraacetic acid (EDTA) is usually added into trypsin to neutralize its enzymatic activity. Trypsin injection into human could induce magnification of chills, fever, headache, dizziness, chest pain, abdominal pain, and diarrhea [13]. The admin-
istration of EDTA could have adverse reactions such as transient dizziness [14], fatigue, and joint pain. In summary, the additions of cell culture including antibiotics, trypsin, and EDTA are all the potential causes of adverse effects to vaccinated animals.

2.4. Binary Ethyleneimine

Inactivation is the most critical step of preparation of inactivated FMD vaccine, and the selection on inactivation agents is also very important for final products. Historically, formalin, crystal violet and N-acetyl ethyleneimine (AEI) were all ever used to prepare FMD vaccine with various concerns. Binary ethyleneimine (BEI) is the currently most commonly used as inactivation agent [15]. The inactivation procedure of BEI treatment for 48 hours at 26°C with final concentration of 3 mmol/L for twice was recommended by “World Organisation for Animal Health” (OIE) in 2006. The concentration of BEI was increased from 1 mmol/L to 3 mmol/L and inactivation temperature was decreased from 30°C to 26°C compared to that recommended by OIE in 2000. And BEI is one of indispensable reagents required for modern vaccine of FMD. The clinical research indicated that BEI demonstrated the efficacy in cancer treatment though accompanied with bone marrow suppression with results of adverse reactions [16] such as nausea, vomiting, loss of appetite, diarrhea, or fever and rash in some individuals. The adverse effect of BEI might be associated with immune response.

2.5. Sodium Thiosulfate

2% Sodium thiosulfate is used in the preparation of inactivated FMD vaccine to neutralize BEI. Sodium thiosulfate, also known as sodium sulfite, caustic soda, and sodium hyposulfite is a white translucent crystalline inorganic compound, $\text{Na}_2\text{S}_2\text{O}_3\cdot5\text{H}_2\text{O}$ with a melting point of 48°C. Sodium thiosulfate is bitter taste, deliquescent, and soluble in water and alcohol. It is commonly used as a reducing agent in chemical production or as a detoxification drug in medicine. The side reaction of sodium thiosulfate manifested in human is dizziness, fatigue, nausea, and vomiting [17], which might be associated with immunological response.

2.6. Contamination in the Cell Culture

Suitable temperature, adequate nutrition, appropriate pH value and non-toxic and sterile environment are all indispensable factors for mammalian cell growth. The microorganism’s contamination of mammalian cells is classified into dominant and recessive contaminations according to the visual inspection. The dominant contamination of BHK-21 ascribed to bacterium, yeast and mold is manifested as medium turbidity, irregular cell morphology and cell disattached from culture petri dish. When high dose of antibiotics is used to inhibit overt contamination, the recessive contamination ascribed to mycoplasma or non-cytopathic virus such as HCV, PCV and PRRSV might be the concern as
well. Though the severity of domination contamination is not visible [18], large amount of endotoxin, a major source of pyrogen, could be produced too; which increases the risk of adverse effect. In addition, recessive contamination could alter physicochemical nature of the host cells with the consequence of incorrect quality control readout.

2.7. Vaccine Adjuvant

There are various types of vaccine adjuvants, and mineral oil is commonly used in China to prepare inactivated FMD vaccine. The injection site could be manifested as redness, swollen, heated and pain after immunization due to the characteristics of mineral oil [19], sticky and difficult to absorb [20]. Though adjuvant Montanide ISA 206 by SEPPIC (Paris, France) could reduce the local adverse reactions after vaccine injection, the problem still remains.

3. Countermeasures

The prophylactic measures before vaccine immunization and timely treatments once the reverse response manifested are mandatory to minimize the reverse response of inactivated FMD vaccination caused lost.

3.1. Prophylactic Measures Pre-Vaccination

The training for vaccination staff should be reinforced to improve professionalism and responsibility, which is important for minimization of adverse reaction in the first place. The vaccination must be carried out according to the instruction and procedure recommended by manufactory strictly. The vaccine is not allowed to be used if it is expired, discoloration, moldy, with clots unable to be dispersed or foreign body, without label or clear tag [21]; and the vaccine stored or transported improperly without entire cold-chain transportation are not allowed to be used; additional, the vaccines without formal approval of production or not produced by qualified manufactures are not allowed to be used as well. For healthy animals with skin lesion, the sterile syringes and prophylactic antibiotics should be used for vaccination, because the lesion skin might increase side effects if the microorganism’s infection through immunization site occurs. Secondly, the proper injection method is required [22]; one syringe for one animal is the prerequisite. Vaccine immunization is a strong stress to animal recipients, and the anti-stress medication and multivitamin addition into the feed water could be considered to reduce the loss due to vaccination stress [23].

The animal recipient should be at healthy condition before vaccination, the recessive infection or disease at latent period sooner, which should be kept into consideration before vaccine immunization. A new batch of vaccine should be tested in a small scale (such as 30 pigs) for three to six days before up-scaled vaccination, to ensure there are no severe adverse responses; and the raising and management on vaccinated animals should be reinforced after vaccination.
3.2. Treatment for Adverse Responses after Vaccination

The timely and swift measures should be taken once the adverse responses discovered. The local treatment could be applied for slightly transient reactions; and the systemic adverse reactions such serious allergy should be treated with injection of epinephrine and dexamethasone [24], and the symptomatic treatment should be used at the same time [25]. For instance, subcutaneous injection of 0.1% adrenaline hydrochloride of 1 mg, and 10% norepinephrine with dose of 2 mg dissolved into 500 mg glucose should be administrated to the recipient with severe adverse responses. Intravenous injection of 5% glucose 500 mg with 1 g vitamin C and 6500 mg vitamin B could be administrated once the symptom alleviated, followed by 5% sodium bicarbonate 500 mg. The assisted respiration, adrenaline injection at multiple sites, and administration of cortisone, compound aminopyrine and compound vitamins could be used for particularly animals with severe adverse response. The animals will be recovered in two days.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


