ARC Journal of Animal and Veterinary Sciences
Volume 5, Issue 1, 2019, PP 24-30
ISSN No. (Online) 2455-2518
DOI: http://dx.doi.org/10.20431/2455-2518.0501004
www.arcjournals.org

Study of In-Vitro Antiviral Activity of Aminoglycosides on Foot and Mouth Disease Virus

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Abstract

Background: *The aminoglycosides family of antibiotics are widely used as a prophylactic measure against bacterial contamination in animal vaccine production.*

Objective: *Screening the antiviral activity of some members of aminoglycosides on foot and mouth disease (FMD) viruses used in the preparation of FMD vaccine in veterinary serum and vaccine research institute (VSVRI) .*

Method: *This study was conducted by in-vitro assessment of cytopathic effect (CPE) and infectivity titers of FMD viruses on Baby hamster kidney (BHK) cells under different concentrations of Neomycin (200, 500 mg/L), kanamycin (200, 500 mg/L), gentamycin (200, 500 mg/L) and streptomycin (200, 500 mg/L) as members of aminoglycosides using the inverted microscope. Positive (aminoglycosides-free) and negative (FMD viruses-free) were used.*

Results: *Our results show that aminoglycosides antibiotics could inhibit the cytopathic effect and reduce the infectivity titers of FMD viruses.*

Conclusion: *Finally we recommend the avoidance of routine inclusion of aminoglycosides antibiotics in tissue culture technique or treating FMD virus suspensions.*

Keywords: *FMD, VSVRI, CPE, BHK.*

1. INTRODUCTION

Since the discovery of penicillin in 1928 many antibiotics including aminoglycosides, b-lactams, fluoroquinolones, and others have been applied clinically for the treatment of many growing number of multidrug-resistant strains of bacteria. Aminoglycosides in particular are being examined to find new compounds or derivatives that might overcome the existing resistant pathogens and prevent or slow the development of novel resistant pathogens.

Aminoglycosides were first established as antibiotics in the 1940s with the discovery of streptomycin and are still widely used worldwide. Aminoglycosides have enjoyed widespread application as chemotherapeutic agents in the treatments of many types of bacterial infections, including both Gram-positive and Gram-negative pathogens ***(Davies and Wright 1997***). The antibacterial mechanism of action of aminoglycosides has been well characterized, and it was discovered in the late 1980s that aminoglycosides' molecular target is the 16S rRNA subunit of the 30S bacterial ribosome ***(Moazed and Noller 1987***).

Although alternative modes of binding have been seen with various aminoglycoside derivatives ***(Kondo et al., 2007*)**, the general interactions of aminoglycosides with three unpaired adenine residues in the decoding loop displaces non-complementary adenines and locks them into a so-called "flipped-out" orientation similar to that ob- served during mRNA decoding ***(Pfister et al., 2003, Vicens and Westhof 2003a, b, Shandrick et al., 2004, Ogle and Ramakrishnan 2005***). Structural examples of these interactions from crystallographic or modeling studies are shown in, which depicts tobramycin, geneticin, amikacin, and paromomycin in complex with A-site oligonucleotides ***(Vicens and Westhof 2001, 2002, 2003a,b, Kondo et al., 2006***). These interactions reduce the fidelity of normal

translational processes by reducing the ability of the ribosome to discriminate between the proper mRNA–tRNA complexes, this leads to the accumulation of truncated or nonfunctional proteins in cells, and eventually to cell death. For a thorough structure-based analysis of the interactions of aminoglycosides with the decoding A-site see the recent review by *(**Francois et al 2005***).

The structurally related aminoglycosides neomycin, paromomycin and gentamycin possess 4,5-substituted and 4,6-substituted 2-deoxystreptamine cores. These compounds exert multiple effects on protein synthesis: they cause mRNA miscoding ***(Davies et al., 1965, 1966***), inhibit mRNA and tRNA translocation ***(Cabanas et al., 1978 and Misumi et al., 1978***, and inhibit ribosome recycling ***(Hirokawa, G. et al 2002***).

Some aminoglycosides are considered to have antiviral activities. Hygromycin B was shown to inhibit replication of herpes simplex virus ***(Lacal et al., 1983)***, mouse hepatitis virus ***(Macintyre et al., 1991a,b)***, HIV type 1 ***(Gatti et al., 1998)***, influenza virus ***(Ghendon et al.,1981)***, and both encephalomyocarditis virus and Semliki forest virus ***(Lacal et al., 1980)***. Neomycin and recently developed neomycin analogs were also demonstrated to inhibit HIV replication and viral entry ***(Zapp et al., 1993; Herold & Spear, 1994; Herold et al., 1994; Hung et al., 2002; Litovchick et al., 2000, 2001; Langeland et al., 1986, 1987)***.

BHK cells are derived from syrian baby hamster kidney (Mesocricetus auratus) (**MacPherson and Stoker 1962**). BHK cells are inherently anchorage dependent cells but also they are applied as suspension, too (**Guo et al., 2015, Hernandez and Brown 2010, Reddy et al., 2016**).

BHK cells are mainly used in animal products, particularly for FMD virus vaccine and rabies vaccine production (**Vester et al., 2010, Park et al., 2010, Aunin 2010, Kallel et al. 2003, Rahman et al., 2007**).

(**Ingrid Kuhlmann 1996)** mentioned that**,** In order to yield reproducable results, antibiotic-free cell culture conditions are necessary. Germ-free cell culture working conditions refer to those conditions which reduce the probability of contamination as much as possible, since absolute sterility is not possible. To achieve this, accurate techniques for sterile cell culture work is necessary.

*(**Lindl and Bauer (1989)** observed that the prophylactic use of antibiotics in tissue culture techniques may cause workers to neglect sterile handling of cell cultures and therefore increase the possibility of development of resistant germs which lead to uncontrollable contaminations.

FMD is an acute contagious viral disease of cloven footed animals ***(Orsel et al., 2007)***. The causative agent is a single stranded positive-sense RNA virus that belongs to the genus Aphthovirus in the family Picornaviridae. There are seven immunologically distinct serotypes of FMD virus, namely; O, A, C,, SAT1, SAT2, SAT3 and Asia1 **(*Belsham, 1993***).

FMD virion has a symmetric protein shell (or capsid) enclosing the genomic RNA. Genome RNA contains a positive single-strand chain approximately 8.3 kb long and encodes a single long open reading frame (ORF) of about 7 kb with two alternative initiation sites. The ORF is flanked by a long 5′-untranslated region (5′-UTR) and a short 3′-UTR, and ends with a genetic- ally encoded poly(A) tail ***(Grubman 1980***). A genome-linked viral nonstructural protein (NSP), 3B (also known as VPg) containing 23–24 amino acid (aa) residues, is covalently bound to its 5′ end, although this protein is rapidly re- leased into an infected cell and is deemed to play no part in translation initiation ***(Lin et al., 2009***). The viral ORF can be translated into a polyprotein of about 250 kDa, which is subsequently cleaved by two virus-encoded proteinases (leader (Lpro) and 3Cpro) to yield structural and NSPs ***(Robertson et al., 1985 and Mason et al., 2003***).

In Egypt, The history of FMD virus goes back to 1950 ***(Mousa et al., 1974)***, when an outbreak caused by serotype SAT2 was reported. Between 1964 and 2005, only serotype O was reported in Egypt **(*Zahran 1960,* and *Farag et al., 2005)***, with the exception of 1972 when type A was introduced from Sub-Saharan Africa (***Knowles et al., 2007***). Series of outbreaks predominantly caused by serotype O, and with a dramatic upsurge in FMD SAT 2 outbreaks during 2012 were reported (***Ahmed et al., 2012, Shawkey et al., 2013***). Serotypes O, A and SAT2 have been circulating in the country since 2012, and Serotype O is considered the predominant serotype (***FAO 2012***).

The objective of this study was to Screen the antiviral activity of some members of aminoglycosides on FMD viruses used in the preparation of polyvalent FMD virus vaccine in VSVRI.

2. Materials and Methods

2.1. BHK Cells

BHK cell line obtained from (FMD department, VSVRI, Egypt) was cultured in Minimal essential medium supplemented with a set of proteins including lactalbumin, treptose phosphate broth were added into this medium, sodium bicarbonate, and 10% newborn calf serum supplied by Capricorn®.

2.2. FMD Virus Strains

Local FMDV strains (O /pan Asia2, A/ Iran 05, SAT2/ Egypt 2012 and SAT2/ Egypt 2018) were isolated and identified by Veterinary Serum and Vaccine Research Institute, Abbasia, Cairo. and confirmed by Pirbright (FMD-WRL), United Kingdom. FMDV were propagated in BHK21 cell line in roller bottles (**Huang et al., 2011)**, Each virus had a infectivity titer of 10^8 50 % tissue culture infective dose /ml (10^8 TCID50/ml) as described by **Reed and Muench (1938).**

2.3. Aminogylcoside Antibiotics

Monitoring the inhibitory effect of neomycin (200, 500 mg/L), kanamycin (200, 500 mg/L), gentamycin (200, 500 mg/L) and streptomycin (200, 500 mg/L) on FMD viruses-induced CPE on BHK cells has been screened using the inverted microscope. Positive (aminoglycosides-free) and negative (FMD viruses-free) were used.

2.4. Inverted Microscope

The CPE of FMD viruses on BHK cells was investigated using the inverted microscope.

3. Results and Discussion

Aminoglycosides are one of the most important classes of antibiotics used in tissue culture technique that inhibit bacterial protein synthesis by targeting the ribosome **(Magnet and Blanchard 2005)**. They are also excellent templates for antibiotic design because of their high binding affinity and properties that allow for broad-spectrum antibacterial activity **(Sutcliffe 2005)**.

The results of 24 hrs-37ºC anti-CPE effect of aminoglycosides on BHK cells infected by 10^8 TCID50/ml of FMD viruses revealed that neomycin (at concentrations ≥ 200 mg/L) inhibits the CPE of FMD viruses on BHK cells as shown in table (1).

Table1. *The CPE (after 24 hrs at 37ºC) of FMD viruses on BHK cells treated by different concentrations of aminoglycosides antibiotics.*

	O /pan Asia2 10^8 TCID50/ml	A/ Iran 05 10^8 TCID50/ml	SAT2/ Egypt 2012 10^8 TCID50/ml	SAT2/ Egypt 2018 10^8 TCID50/ml
Neomycin (200 mg/L)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Neomycin (500 mg/L)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Kanamycin (200 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Kanamycin (500 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Gentamycin (200 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Gentamycin (500 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Streptomycin (200 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Streptomycin (500 mg/L)	**CPE**	**CPE**	**CPE**	**CPE**
Negative control (No virus)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Positive control (No antibiotics)	**CPE**	**CPE**	**CPE**	**CPE**

So that, neomycin (at concentrations ≥ 200 mg/L) has In-vitro antiviral action against FMD viruses.

These results were in agreement with ***Langeland et al., 1986, 1987, Zapp et al., 1993, Herold and Spear 1994, Herold et al., 1994, Litovchick et al., 2000, 2001, Hung et al., 2002 and Smita et al. 2018*** who mentioned that the neomycin has mediated a potent antiviral effect.

The effect of aminoglycosides on The 24 hrs-37ºC infectivity titers expressed as TCID50/ml of FMD viruses treated by different concentrations of aminoglycosides antibiotics starting as 10^8 TCID50/ml revealed that all the aminoglycosides

in this study affect infectivity titers (expressed as TCID50) except streptomycin (at concentrations ≤ 500 mg/L) as shown in table (2).

Table2. *The infectivity titers expressed as TCID50/ml (after 24 hrs at 37ºC) of FMD viruses treated by different concentrations of aminoglycosides antibiotics starting as 10^8 TCID50/ml.*

	O /pan Asia2 10^8 TCID50/ml	A/ Iran 05 10^8 TCID50/ml	SAT2/ Egypt 2012 10^8 TCID50/ml	SAT2/ Egypt 2018 10^8 TCID50/ml
Neomycin (200 mg/L)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Neomycin (500 mg/L)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Kanamycin (200 mg/L)	**10^6 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**
Kanamycin (500 mg/L)	**10^6 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**
Gentamycin (200 mg/L)	**10^7 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**	**10^6 TCID50/ml**
Gentamycin (500 mg/L)	**10^6 TCID50/ml**	**10^5 TCID50/ml**	**10^5 TCID50/ml**	**10^5 TCID50/ml**
Streptomycin (200 mg/L)	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**
Streptomycin (500 mg/L)	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**
Negative control (No virus)	**NO CPE**	**NO CPE**	**NO CPE**	**NO CPE**
Positive control (No antibiotics)	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**	**10^8 TCID50/ml**

These results were in agreement with ***Lacal et al., 1980,1983, Macintyre et al., 1991a,b, Ghendon et al., 1981 and Gatti et al., 1998*** who mentioned that the neomycin inhibit RND viruses replication and viral entry.

In this work we studied the In-vitro effects of Aminoglycosides antibiotics on FMD viruses used in preparation of polyvalent FMD vaccine in VSVRI in Egypt. The effects concerned in this study we CPE formation on BHK cells and infectivity titers.

The antibacterial mechanism of action of aminoglycosides has been well characterized, and it was discovered in the late 1980s that aminoglycosides molecular target is the 16S rRNA subunit of the 30S bacterial ribosome ***Moazed and Noller 1987.***

The results revealed that aminoglycosides antibiotics have In-vitro dose and member-dependant antiviral activity against FMD viruses. Theses results are supported by ***Lai et al., 2004; Konno et al., 2004; Borovinskaya et al., 2007a,b, Cabanas et al., 1978; Eustice and Wilhelm, 1984*** who mentioned that the natural and synthesized aminoglycoside-based antibiotics inhibit viral translation, resulting in a decrease of viral RNA synthesis and can be a potent tool to explore and develop new specific antiviral drugs against pathogenic RNA viruses.

Our results are also confirmed by **Ingrid Kuhlmann (1996)** who mentioned that the prophylactic use of antibiotics risks neglect of sterile technique. Moreover, antibiotics may have side effects on the cells. Consequently, the prophylactic use of antibiotics may effect the results of experiments.

Finally we recommend the avoidance of using aminoglycosides antibiotics (except streptomycin at concentration ≤ 500 mg/L) in treating FMD virus suspensions or isolation of FMD viruses as it may weaken or even inhibit these RNA viruses. Also the routine inclusion of aminoglycosides antibiotics in tissue culture technique is contraindicated.

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Citation: *Assem A Mohamed. Study of In-Vitro Antiviral Activity of Aminoglycosides on Foot and Mouth Disease Virus. ARC Journal of Animal and Veterinary Sciences. 2019; 5(1):24-30. doi: dx.doi.org/10.20431/2455-2518.0501004.*