Antimycobacterial Activity of Veterinary Antibiotics (Apramycin and Framycetin) against Mycobacterium abscessus: Implication for Patients with Cystic Fibrosis

John E. Moore1,2,3, Greg Koulilanos4, Margaret Hardy5, Naoaki Misawa4,6, B. Cherie Millar1,2,3
1Department of Bacteriology, Northern Ireland Public Health Laboratory, Belfast City Hospital, 2School of Biomedical Sciences, Ulster University, 3Centre for Experimental Medicine, Queen’s University, 4St. David’s Poultry Team, Dungannon Enterprise Centre, Northern Ireland, UK, 5Department of Veterinary Medical Science, Laboratory of Veterinary Public Health, Faculty of Agriculture, University of Miyazaki, 6Center for Animal Disease Control, University of Miyazaki, Miyazaki, Japan

Abstract

Background: Antimicrobial resistance has rendered certain species of Mycobacterium difficult to treat clinically, particularly the nontuberculous Mycobacterium and Mycobacterium abscessus. While veterinary medicine and human medicine share many classes of antibiotics, there are several antibiotics which are uniquely licensed to veterinary medicine but not human medicine. It was, therefore, the aim of this study to examine the action of eight veterinary antibiotics to a population of multi- and pan-resistant M. abscessus, isolated from the sputum of patients with cystic fibrosis (CF). Methods: Antibiotic susceptibility studies were performed on human clinical isolates of M. abscessus (n = 16), including 11 smooth isolates, 4 rough isolates, and 1 reference isolate (NCTC 13031), against the following 7 veterinary antibiotics (antibiotic class): apramycin (aminoglycoside), cefocevin (cephalosporin), ceftriaxone/ceftriaxone (cephalosporin), framycetin (aminoglycoside), lincomycin (lincosamide), pirlimycin (lincosamide), and spectinomycin (aminocyclitol). Results: M. abscessus isolates were sensitive (100%) to apramycin and framycetin but resistant (100%) to cefocevin, ceftriaxone, lincomycin, pirlimycin, and spectinomycin. Conclusion: This study identified that the veterinary aminoglycosides, apramycin, and framycetin, have in vitro activity against multi-resistant clinical isolates of M. abscessus. Further studies should now compare the activity of these antibiotics against amikacin and the human aminoglycoside, advocated in the treatment of disease in CF patients, to determine if these novel antibiotics have a future role for the development in human medicine with such chronic disease patients.

Keywords: Cystic fibrosis, Mycobacterium abscessus, respiratory, veterinary antibiotic, zoonosis

Introduction

The long-term use of several classes of antibiotic agents, including aminoglycosides, beta-lactams, fluoroquinolones, macrolides, and polymyxin, for the prophylaxis, maintenance, and treatment of bacterial respiratory pathogens causing chronic chest infections in patients with cystic fibrosis (CF) has important consequences for the persistence of respiratory pathogens, including the emerging nontuberculous mycobacteria, in particular, Mycobacterium abscessus. M. abscessus infection in patients with CF has gradually emerged from early reports of its prevalence of 1.3% in 1984[1] to 32.7% in adult CF patients in the US[2] although prevalence rates from the US Cystic Fibrosis Foundation Registry are 12%.1.3] This infection is associated with chronic persistence of the organism in the lower airways, once colonization has occurred, leading to increased morbidity and mortality in some patients.[4] Furthermore, the presence of this organism in patients’ sputum is usually a contraindication for lung transplantation. Hence, it is important to be have efficacious antibiotics available to attempt to eradicate the organism on the first isolation from sputum, as well as to chronically manage the organism, particularly with acute pulmonary exacerbation. One

Access this article online

Quick Response Code: [QR Code]
Website: www.ijmyco.org
DOI: 10.4103/ijmy.ijmy_73_18

Address for correspondence: Prof. John E. Moore, Department of Bacteriology, Northern Ireland Public Health Laboratory, Belfast City Hospital, Belfast, BT9 7AD, Northern Ireland, UK.
E-mail: jemoore@niphl.dnet.co.uk

How to cite this article: Moore JE, Koulilanos G, Hardy M, Misawa N, Millar BC. Antimycobacterial activity of veterinary antibiotics (apramycin and framycetin) against Mycobacterium abscessus: Implication for patients with cystic fibrosis. Int J Mycobacteriol 2018;7:265-7.
worrying microbiological characteristic to emerge from studies to date is the relative antibiotic resistance of this organism, where there is usually a high degree of antibiotic resistance to several classes of antibiotics.\[5\] Therefore, it was the aim of the current study to explore the potential antimycobacterial activity of veterinary antibiotics, which are used in veterinary medicine.

**Methods**

*M. abscessus* isolates (*n* = 16) were obtained from the HSC Microbiology Culture Repository, MicroARK (www.microark.com), housed at the Northern Ireland Public Health Laboratory, at the Belfast City Hospital. These isolates consisted of 15 clinical isolates obtained from patients with CF and 1 reference strain (NCTC 13031) obtained from the National Culture Type Collection, Public Health England (Colindale, London, UK). All isolates had been historically stored on slopes of Lowenstein–Jensen medium in glass universal containers at ambient temperature. All isolates were recovered and passaged twice on Columbia Agar Base (Oxoid CM0331; Oxoid Ltd., Basingstoke, UK) supplemented with 5% (v/v) defibrinated horse blood, which was incubated at 37°C for 5 days, before employment in the current study. A fresh culture of each isolate was prepared as described above and was harvested into 0.1% (w/v) peptone saline (CM0733) to yield a 0.5 McFarland inoculation standard. Inoculum was streaked onto fresh Columbia Agar Base (Oxoid CM0331) supplemented with 5% (v/v) defibrinated horse blood and allowed to dry. Standard disk-diffusion assays were performed on each isolate, with seven antibiotics (Oxoid Ltd., Basingstoke, UK), including apramycin (15 µg disk) (aminoglycoside), cefovecin (30 µg) (cephalosporin), ceftiofur (30 µg) (cephalosporin), framycetin (100 µg) (aminoglycoside), lincomycin (2 µg) (lincosamide), pirlimycin (2 µg) (lincosamide), and spectinomycin (10 µg) (aminocyclitol) [Figure 1]. All plates were incubated aerobically at 37°C for 5 days, before reading. Antibiotic susceptibility was reported as resistant (R), with bacterial growth to the edge of the antibiotic disk or sensitive (S), with a zone of inhibition of at least 5-mm radius.

**Results**

*M. abscessus* isolates were sensitive (100%) to apramycin and framycetin but resistant (100%) to cefovecin, ceftiofur, lincomycin, pirlimycin, and spectinomycin.

**Discussion**

This study demonstrated antimycobacterial activity of two antibiotics, commonly used in veterinary medicine, namely, apramycin and framycetin. All *M. abscessus* isolates tested were sensitive to these antibiotics. All other antibiotics examined from the cephalosporin, lincosamide, or aminocyclitol classes did not show any antimycobacterial activity against any of the isolates tested. Interestingly, there was no activity with streptomycin, which is an aminocyclitol antibiotic, which is closely related to the aminoglycosides.

Apramycin is currently licensed in the UK by the Veterinary Medicines Directorate for pigs, cattle, rabbits, and chickens, either as (i) a premix for medicated feedstuff (200 g/kg, 100,000 IU/g, 100 g/kg) or (ii) a soluble powder for oral solution. The indications for usage include (a) the treatment and control of bacterial enteritis in young pigs caused by *Escherichia coli* and other apramycin-sensitive organisms, (b) the treatment of bacterial enteritis associated with organisms susceptible to apramycin in pigs, colibacillosis, and salmonellosis in calves *E. coli* septicemia in young chickens, and (c) the treatment in pigs and metaphylaxis of bacterial enteritis caused by
microorganisms susceptible to apramycin such as *E. coli* and for the reduction in mortality in rabbits and clinical signs related to epizootic enterocolitis due to *E. coli* (http://www.vmd.defra.gov.uk/ProductInformationDatabase/Default.aspx). Apramycin has been shown previously to be efficacious in the treatment of *Mycobacterium tuberculosis* in a murine infection model, with superior kill kinetics compared to the human aminoglycoside and amikacin. In addition, it has been reported as being less ototoxic than amikacin, which would make a potentially attractive alternative, especially when used continuously.

Likewise, framycetin is also an aminoglycoside antibiotic, which has indications in veterinary medicine, for cats, dogs, and cattle, for topical, intramammary, and intratreatment of (i) otitis externa including the ear mite, *Otodectes cynotis*, infestation dogs, and cats, (ii) as an adjunct to intramammary therapy in the treatment of acute bacterial mastitis with systemic involvement, caused by organisms sensitive to framycetin in dairy cows. *In vitro*, framycetin has shown activity against *E. coli*, *Staphylococcus aureus*, *Arcanobacterium pyogenes*, and *Klebsiella* spp. and (iii) for treatment of subclinical mastitis at drying off and the prevention of new bacterial infections of the udder during the dry period in dairy cows, caused by bacteria susceptible to penicillin and framycetin. To date, there have been no reports on antimycobacterial activity of framycetin against the mycobacteria.

At the present, as there are no interpretive criteria, including EUCAST or CLSI, to help determine antibiotic breakpoints for these two aminoglycoside antibiotics and *M. abscessus*, fundamental/basic science studies and pharmacokinetic/pharmacodynamics studies are now required to estimate the potential value of such antibiotics entering human medicine for nebulized or intravenous treatment of *M. abscessus* chronic infection and aiding their assessment by the human medicine drug regulators, including the Food and Drug Administration and the European Medicines Agency.

Given the increasing burden of antimicrobial resistance globally, particularly with the mycobacteria, it is, therefore, important to explore all potential sources of antibacterial activity and their potential route to successful registration and employment, to strengthen society’s arsenal of availability antibiotics.

**Conclusion**

This study has identified that the veterinary aminoglycosides, apramycin and framycetin, have *in vitro* activity against multi-resistant clinical isolates of *M. abscessus*. Further studies should now compare the activity of these antibiotics against amikacin, the human aminoglycoside, advocated in the treatment of disease in CF patients, to determine if these novel antibiotics have a future role for the development in human medicine.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Smith MJ, Efthimiou J, Hodson ME, Batten JC. Mycobacterial isolations in young adults with cystic fibrosis. Thorax 1984;39:369-75.
2. Rodman DM, Polis JM, Heltshe SL, Sontag MK, Chacon C, Rodman RV, et al. Late diagnosis defines a unique population of long-term survivors of cystic fibrosis. Am J Respir Crit Care Med 2005;171:621-6.
3. Salsgiver EL, Fink AK, Knapp EA, LiPuma JJ, Olivier KN, Marshall BC, et al. Changing epidemiology of the respiratory bacteriology of patients with cystic fibrosis. Chest 2016;149:390-400.
4. Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: Executive summary. Thorax 2016;71:88-90.
5. Benwill JL, Wallace RJ Jr. *Mycobacterium abscessus*: Challenges in diagnosis and treatment. Curr Opin Infect Dis 2014;27:506-10.
6. Meyer M, Freihofer P, Scherman M, Teague J, Lenaerts A, Böttger EC. *In vivo* efficacy of apramycin in murine infection models. Antimicrob Agents Chemother 2014;58:6938-41.