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REVIEW ARTICLE

Update on new medicinal applications of gentamicin: Evidence-based review

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Gentamicin (GM) was discovered in 1963 and was introduced into parenteral usage in 1971. Since then, GM has been widely used in medicinal applications. The Food and Drug Administration of the United States approved the routine prescription of GM to treat the following infectious disorders: infection due to *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Citrobacter* spp., *Enterobacteriaceae* spp., *Pseudomonas* spp.; *Staphylococcus* infectious disease; bacterial meningitis; bacterial sepsis of newborns; bacterial septicemia; infection of the eye, bone, skin and/or subcutaneous tissue; infective endocarditis; peritoneal dialysis–associated peritonitis due to *Pseudomonas* and other gram-negative organisms; peritonitis due to gastrointestinal tract infections; respiratory tract infections; and urinary tract infectious disease. GM is an old antibiotic and is used widely beyond its FDA-labeled indications as follows: actinomycotic infection; *Staphylococcus saprophyticus* bacteremia with pyelonephritis; appendicitis; cystic fibrosis; diverticulitis; adjunct regimen for febrile neutropenia; female genital infection; uterine infection; postnatal infection; necrotizing enterocolitis in fetus or newborn; osteomyelitis; pelvic inflammatory disease; plague; gonorrhea; tularemia; prophylaxis of post-cholecystectomy infection, transrectal prostate biopsy, and post–tympanostomy-related infection; malignant otitis externa; and intratympanically or transtympanically for Ménière's disease. GM is also used in combination regimens, such as with beta-lactam antibiotics to treat mixed infection and with bacteriophage to treat *Staphylococcus aureus* infections. It is also added to medical materials, such as GM-loaded cement spacers for osteomyelitis and prosthetic joint–associated infections. Overall, there are many medicinal applications for GM. To reduce the development of GM-resistant bacteria and to

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maintain its effectiveness, GM should be used only to treat or prevent infections that are proven or strongly suspected as being caused by susceptible bacteria. In the future, we believe that GM will be used more widely in combination therapy and applied to medical materials for clinical applications. A definitive, appropriately powered study of this antibiotic and its clinical applications is now required, especially in terms of its effectiveness, safety, and cost.

Introduction

Gentamicin (GM) is an aminoglycoside that is widely used in clinical conditions to fair clinical response. It was isolated from *Micromonospora* in 1963, proving to be a breakthrough in the treatment of gram-negative (GN) bacillary infections, including those caused by *Pseudomonas aeruginosa*. It was introduced into parenteral usage in 1971. GM has been widely used in medicinal applications since then. In the past 50 years, the clinical outcome of GM use has mostly been good, but the opposite was sometimes true. Due to the progression of pharmaceuticals, the prescription of GM has decreased. Based on clinical experience where the response to GM is good, the United States (US) Food and Drug Administration (FDA) approved the use of GM for treating the following infectious disorders[1]: infection by *Klebsiella pneumoniae*, *Escherichia coli*, *Serratia marcescens*, *Citrobacter* spp., *Enterobacteriaceae* spp., or *Pseudomonas* spp.; *Staphylococcus* infectious disease; bacterial meningitis; bacterial sepsis of newborns; bacterial septicemia; infection of the eye, bone, skin, and/or subcutaneous tissue; infective endocarditis; peritoneal dialysis-associated peritonitis due to *Pseudomonas* and other GN organisms; peritonitis due to gastrointestinal tract infections; respiratory tract infection; and urinary tract infectious disease. GM is also used widely beyond its FDA-labeled indications as follows[1]: actinomycotic infection; *Staphylococcus saprophyticus* bacteremia with pyelonephritis; appendicitis; cystic fibrosis (CF); diverticulitis; adjunct regimen for febrile neutropenia; female genital infection; uterine infection; peripartum and postnatal infection; necrotizing enterocolitis in the fetus or newborn; osteomyelitis; pelvic inflammatory disease; plague; gonorrhea; tularemia; prophylaxis of post-cholecystectomy infection, transrectal prostate biopsy, and post-tympanostomy-related infection; malignant otitis externa; and intratympanically or transtympanically for Ménière's disease (MD). GM is also used in combination regimens, such as with beta-lactam antibiotics, to treat mixed infections and with bacteriophage to treat *Staphylococcus aureus* infections. GM is also added to medical materials, such as GM-loaded cement spacers for osteomyelitis and prosthetic joint-associated infections (PJIs). The application of GM has changed in recent years.

This review aims to provide physicians and pharmacists with a review of GM and its role in the treatment of infectious diseases, with a focus on its medicinal applications. There is more than 50 years' worth of cumulative clinical experience behind GM; as less adverse reactions are reported, and it is inexpensive and convenient, GM continues to play an important role in the treatment and prophylaxis of infectious and non-infectious diseases, even in the face of patient-centered treatment, quality of medical care in general, resistant microorganisms, cost-benefit limitations, and overall medical expenses.

GM exerts concentration-dependent bactericidal actions and is active against a wide range of aerobic GN bacilli. GM is also active against staphylococci and certain mycobacteria. It is effective even when the bacterial inoculum is large, and resistance rarely develops during the course of treatment. Due to its potency, GM is used as prophylaxis and treatment in a variety of clinical situations. Over the course of half a century, GM has been used in the treatment and prophylaxis of infectious and non-infectious diseases that constitute more than 40 clinical conditions. We have divided the use of GM into FDA-approved and non-FDA-approved labeling indications.[1] These indications are summarized in Supplement 1. Its FDA-approved labeling indications included at least 18 clinical conditions and the non-FDA-approved labeling indications include at least 27 clinical conditions. As the clinical data were limited, the use of GM for these non-FDA-approved labeling indications was controversial. However, clinical studies in this field over the past decade have reported fair responses in the accumulated clinical experiences of GM; therefore, the use of GM in the above clinical conditions has been accepted.

Over the past 50 years, GM was sometimes used for non-FDA-approved labeling indications because of bad clinical responses to traditional treatment, the availability of preliminary results only (e.g., the results of clinical experience or from animal studies but not approved by the FDA), and low medical cost. Due to limited evidence-based information, the use of GM for such indications was controversial. As clinical studies from the past 10 years have reported fair responses to the accumulative clinical experiences of GM, it remains an important option for the above clinical conditions. We reviewed the literature from the past 10 years, and summarized the clinical conditions in Tables 1 and 2.[3,7,8,11,21,22,24–26,28–30,34,36,40–42,45,50,52,53,56,61,62,65,68,72,76] We divided the indications for GM according to dosage form, and describe the indications and review articles in accordance with this division in the following sections.

Parenteral GM

S. saprophyticus is generally susceptible to most antibiotics, including penicillin (PEN).[2] Forrest et al[2] demonstrated significantly high failure rates for single-dose PEN therapy. In our clinical experience, GM is one option that can be used to treat *S. saprophyticus* infection.[3] *Bartonella quintana*